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8–12 September 2017, Madrid, Spain

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ESMO is the leading professional organisation for medical oncology, with the overarching goal of improving outcomes for cancer patients everywhere. We are the society of reference for oncology education and information, and are committed to supporting our members to develop and advance in a fast-evolving professional environment.

Founded in 1975, ESMO has European roots with a global reach: we welcome oncology professionals from around the world. We are a home for all oncology stakeholders, connecting professionals with diverse expertise and experience, and speaking with one voice for our discipline. Our education and information resources support an integrated multi-professional approach to cancer care, from a medical oncology perspective. We seek to erase boundaries in cancer care, whether between countries or specialities, and pursue our mission across oncology, worldwide.

The ESMO community brings together more than 16,000 oncology professionals from over 130 countries. Drawing on 40 years of experience and around 500 expert committee members, ESMO serves its members and the oncology community through:

• Post-graduate oncology education and training
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• Continuously reviewed, evidence-based standards for cancer care in Europe
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Cancer care is rapidly becoming more integrated and more specialised; whether their field is research, diagnosis, treatment, care, or advocacy, oncology professionals need to both build their specialist knowledge and connect with the best practitioners in other disciplines worldwide. ESMO membership makes this possible.

Please visit esmo.org to learn more. Across Oncology. Worldwide.

The European Association for Cancer Research (EACR)

The European Association for Cancer Research is a professional membership society for cancer researchers with more than 10,000 members worldwide. The EACR was founded in 1968 and has one guiding aim: ‘The advancement of cancer research for the public benefit’. Membership is open to anyone actively working or studying in cancer research. Our members work across the full spectrum of the field, from basic through to translational and clinical research, and range from postgraduate students to winners of the Nobel Prize. Researchers who are members of one of the 14 EACR affiliated ‘National Societies’ automatically become members of the EACR as part of the wider benefits of belonging to their national society. The membership fee for active members is just 40 Euros per annum or 120 Euros for 4 years, and special reduced membership fees are available to postgraduate students and those with less than 4 years’ post-doctoral experience.

We facilitate communication and collaboration within the cancer research community. We also set out to raise the profile of cancer research in Europe and to make the case for sustained political and economic support. We organise scientific conferences of the highest quality, open to members and non-members. Our Conference Series of small, focused meetings is highly regarded for its focus on the latest research topics and for the provision of opportunities for interaction between speakers and participants. In 2018 we will celebrate our 50th anniversary and invite you to join us at EACR25, our biennial Congress to be held in Amsterdam, Netherlands, 30 June - 03 July 2018.

Find out more about the EACR at www.eacr.org
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Background: Mutations in KRAS are the most frequent RAS alterations in human cancer and the prevalent driver event in lung adenocarcinoma (LUAD). There are no effective targeted therapies for KRAS-driven LUAD and chemotherapy remains the standard of care. Small-molecule inhibitors of the MAPK pathway, one of the prominent downstream KRAS mediators, show minimal clinical activity either as single agents or in combination with chemotherapy. Recently, wild-type KRAS (KRAS\textsuperscript{WT}) was shown to enhance tumor fitness in KRAS mutant AML and CRC cell lines while concurrently inhibiting sensitivity to MEK inhibition between KRAS proteins could be a key regulator for lung adenocarcinoma biology and determinant of treatment response.

Methods: To study the role of wild-type KRAS in the context of KRAS-driven cancer cells, we used genetically inducible models of KRAS loss of heterozygosity (LOH). We developed an isogenic KRAS\textsuperscript{WT}/null inducible system that lacks endogenous Hras/Nras but harbors conditional CRE/\textsuperscript{Cre}, controlled KRas\textsuperscript{G12D} alleles. Furthermore, we reconstituted KRAS\textsuperscript{WT}/null in KRAS-driven murine and human LUAD cell lines lacking the wild-type KRAS allele and evaluated the in vitro and in vivo impact on tumor progression and response to MEK inhibition.

Results: KRAS\textsuperscript{WT} decreased in vitro and in vivo fitness of human and murine KRAS mutant LUAD tumor cells. However, this phenotype was reverted upon MEK inhibition, with KRAS LOH cells being more sensitive than KRAS\textsuperscript{WT} expressing cells. Interestingly, both effects were dependent on wild-type/mutant KRAS dimerization and not observed with the dimerization-deficient KRAS\textsuperscript{D154Q}. We provide a mechanistic model of the ambivalent function of KRAS\textsuperscript{WT}, linking its tumor suppressor function with increased MEK inhibitor resistance through dimerization with mutant KRAS.

Conclusions: 1) KRAS\textsuperscript{WT} affects cellular fitness in KRAS-driven LUAD \& KRAS\textsuperscript{WT} inhibitory effect is dependent on dimerization with mutant KRAS \& Impaired wild-type/mutant KRAS dimerization restores sensitivity to MEK inhibitors in vivo.

Legal entity responsible for the study: Dana Farber Cancer Institute

Funding: Stand Up To Cancer - American Cancer Society Lung Cancer Dream Team Translational Research Grant (Grant Number: SU2C-AACR-DT17-15)

Disclosure: J. Kohler: Received consultant honoraria from Boehringer Ingelheim for writing and publishing two review articles on alatinub and travel grants from Roche, Amgen and Lilly. K.D. Westover: Reports receiving a commercial research grant from Astellas Pharmaceuticals. P.A. Jänne: Stock Ownership: Gatekeeper Pharmaceuticals Advisory Role: AstraZeneca, Boehringer Ingelheim, Pfizer, Chugai Pharmaceutical, ARIAD Pharmaceuticals, Merrimack Pharmaceuticals, Roche, Genentech, Lung Oncology, Igynta Research Funding: Astellas Pharma, AstraZeneca. All other authors have declared no conflicts of interest.
However, the detailed molecular mechanisms of GGNBP2 and its role in triple negative breast cancer (TNBC) remain largely unclear.

Methods: A human breast cancer tissue array containing 138 human breast tissue samples was utilized to examine GGNBP2 expression in breast cancer samples by IHC. To address the potential anti-breast cancer role of GGNBP2 in vitro, we expressed exogenous GGNBP2 in TNBC cells, including MDA-MB-231 and Cal51 cell lines. Cell proliferation and cell cycle were assessed by cell growth curve/EdU assays and flow cytometry after propidium iodide staining. Apoptosis was determined by flow cytometry after annexin V staining, by caspase 3/7 and caspase 9 activity assays. Cancer stem cell properties were determined by expression of CD44/CD24/ALDH1 markers. The levels of phosphorylated STAT3 and total STAT3 were determined by western blot. Quantitative PCR and Western blot were carried out to evaluate the effects of GGNBP2 overexpression on STAT3 target genes, CCND1, Mcl-1, survivin, bax and bim expression.

Results: GGNBP2 expression is down-regulated in TNBC cells and patient tumors and is associated with poor patient survival. Overexpression of GGNBP2 significantly induces cell cycle G0/G1 phase arrest and apoptosis in TNBC cells. Expression of cancer stem cell markers also decreased in GGNBP2-overexpressed TNBC cells. GGNBP2 reduces the expression levels of CCND1, Mcl-1 and survivin, promotes the expression levels of bax and bim proteins. Importantly, overexpression of GGNBP2 inhibits STAT3 phosphorylation and STAT3 downstream target gene expression, including CCND1, Mcl-1, survivin.

Conclusions: GGNBP2 serves as a critical nuclear negative regulator of STAT3-mediated gene expression and tumorigenesis.

Legal entity responsible for the study: Jin Zhang

Funding: None

Disclosure: All authors have declared no conflicts of interest.

SPD | The acquired resistance to the combination of the anti-EGFR cetuximab and an MEK inhibitor refametinib in KRAS mutated colorectal cancer cell lines depends on PI3K-signalling


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Background: Previous studies showed that the combination of an anti-epidermal growth factor (EGFR) and a selective MEK1/2-inhibitor displays a significant anti-tumour activity in RAS-wild type colorectal cancers (CRCs), while the same combination par-
tially reverses anti-EGFR primary resistance in KRAS mutated colorectal cancer cell lines. However, mechanisms of resistance to this combination are still unclear.

Methods: We generated KRAS mutated CRC cell lines (HCT15 and HCT116) resistant to a combination of cetuximab (an anti-EGFR antibody) and 8 nylon

Results: We found consistent hyperactivation of the PI3K-AKT pathway and concurrent inactivation of the MAPK pathway, coupled to the activation of multiple RTKs of the HER family such as HER2 and HER3 in resistant cells when compared to parental cells. Treatment with GDC-0941 was able to partially restore the sensitivity to the drug combination, suggesting a central role for this pathway in mediating resistance in this setting, while alatinib was not capable of reverting the resistant phenotype when used alone but showed synergistic activity when combined to GDC-0941.

Conclusions: These preliminary results suggest that PI3K activation plays a central role in the acquired resistance to the combination of anti-EGFR and MEK1-PI3K activation depends at least in part by the activation of the HER family of RTK, but it can also be activated by other receptors. In vivo experiments on mice are currently ongoing.

Legal entity responsible for the study: University of Campania “L. Vanvitelli”

Funding: Associazione Italiana per la Ricerca sul Cancro (AIRC)

Disclosure: All authors have declared no conflicts of interest.
Conclusions: Our results provide strong supports that epigenetic modification is associated with maintenance of properties of BCSCs and reveal that GSKJ4 is capable to be a prospective agent targeting BCSCs.

Legal entity responsible for the study: None

Funding: None

Disclosure: All authors have declared no conflicts of interest.

**8P** The impact of kynurenine-mediated oxidative stress on the survival of human breast cancer stem cells (CD24+/CD44+)

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Background: Cancer stem cells (CSCs) have been proven to be tumorigenic and may be responsible for the resistance to chemo-radiotherapy treatment, disease recurrence and metastasis. Chemo-radiotherapy therapy modulates oxidative stress in cancer cells, leading to cellular adaption response including modulation of cell survival and antioxidant defense mechanisms. However, the redox status alteration of breast CSCs is not yet clearly understood. The aim of this study was to elaborate the impact of kynurenine-mediated oxidative stress on the survival of human breast CSCs (CD24+/CD44+) which might be beneficial to understand the underlying mechanism of chemo-radiotherapy treatment resistance.

Methods: Human breast CSCs (CD24+/CD44+) and non-CSCs (CD24−/CD44−) were treated with rotenone and DMSO (vehicle) for 6 hours, respectively. The effects of rotenone on oxidative stress were assessed by analysing intracellular reactive oxygen species (ROS) level using dihydroethidium assay, as well as mRNA expression and specific activity of MnSOD antioxidant. Finally, cell survival was determined using MTS assay, as well as through analysis of survival mRNA expression.

Results: Our results showed that rotenone could not modulate the superoxide level of human breast CSCs (CD24+/CD44+) in contrast to that of non-CSCs (CD24−/CD44−). Albeit MnSOD expression has been excessively enhanced by rotenone treatment, the enzyme activity was still lower than in non-CSCs. Importantly, the cell viability of CSCs was higher than that of non-CSCs, which related to the increase of survivin.

Conclusions: We conclude that human breast CSCs (CD24+/CD44+) could survive better than their counterpart non-CSCs (CD24−/CD44−) when treated with rotenone. This impact might be associated with the increase of antioxidant MnSOD expression and survivin mRNA expression.

Legal entity responsible for the study: Faculty of Medicine, Universitas Indonesia

Funding: None

Disclosure: All authors have declared no conflicts of interest.

**9P** Kynurenine-3-monooxygenase (KMO) protein promotes triple negative breast cancer progression


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Background: Triple-negative breast cancer (TNBC) remains a difficult-to-treat cancer and the biology beneath TNBC is a research interest. Tryptophan-kynurenine metabolite plays an important role in epithelial-mesenchymal transition (EMT), cancer stem cells (CSCs) and immune escape. Previous studies have focused on the expression and function of the first step and the rate-limiting enzyme in tumor cells, whereas the second step catalytic enzyme kynurenine-3-monooxygenase (KMO) was rarely addressed in tumorigenesis. Hence, we sought to investigate the mechanism and functions of KMO in TNBC carcinogenesis.

Methods: KMO gene alteration and mRNA transcripts were analyzed from The Cancer Genome Atlas (TCGA) database. MDA-MB-231 and MDA-MB-468 TNBC cell lines were used for in vitro studies. Cell proliferation, colony formation, transwell migration/invasion assays and tumorsphere forming ability were used for functional study. Signal transduction pathways were assessed by Western blot, quantitative real-time PCR and reporter assays. The effect of KMO on tumor growth was tested in nude mice with breast cancer xenografts.

Results: TCGA analysis showed high-frequency of KMO amplification alterations, which was related to poor overall survival in breast cancers. KMO transcripts were upregulated in the tumor tissues of breast cancers, especially in TNBC. The functional assays showed that ectopic KMO expression promoted tumorigenesis, including cell growth and abilities of colony formation, migration, invasion, and tumorsphere formation. Moreover, western blot analysis revealed expressions of epithelial marker E-cadherin were decreased and mesenchymal markers N-cadherin, and Twist were increased by KMO overexpression. Interestingly, the mRNA and protein levels of pluripotency genes including CD44, Nanog, Oct4, and Sox2 were also upregulated by KMO knockdown. Data of reporter gene assay showed that the activities of Nanog, Oct4, and Sox2 promoters were enhanced by KMO overexpression.

Furthermore, knockdown KMO decreased the xenografted tumor growth of MDA-MB-468 cells, suggesting its oncogenic role in TNBC.

Legal entity responsible for the study: Taipei Veterans General Hospital

Funding: Taipei Veterans General Hospital

Disclosure: All authors have declared no conflicts of interest.

**10P** PIM1 kinase promotes cell migration via SHP2 in triple-negative breast cancer

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Background: Triple-negative breast cancers (TNBCs) are aggressive and associated with poor prognosis. We have recently demonstrated that PIM1 regulates cell death, tumour growth and chemotherapy response in TNBC. This study aims to further explore the molecular mechanisms by which PIM1 promotes malignant phenotypes in TNBC, in particular cell migration.

Methods: The HumanHT-12 v4 expression array was used to interrogate changes in gene expression upon PIM1 knockdown in TNBC cell lines. Transwell migration assays and time-lapse live-cell imaging were used to study the role of PIM1 in cell migration. To assess the morphology of TNBC cells we stained F-actin with 488-phalloidin. Phospho-kinase arrays were used to elucidate the pathway by which PIM1 may control cell migration.

Results: Gene expression analysis revealed PTPN11 as the most downregulated gene upon PIM1 knockdown in TNBC cell lines. These results were validated by qRT-PCR in 3 TNBC cell lines. PTPN11 encodes for the phosphatase SHP2, known to be relevant for the migration of TNBC cells. We therefore studied whether PIM1 was also associated to this phenotype in TNBC cell lines. PIM1 knockdown led to a defect on 2D-transwell migration in MDA-MB-231 and SUM159 cells, similar to that observed upon SHP2 knockdown. Interestingly, SHP2 knockdown did not affect short-term cell population growth of TNBC cells, suggesting that PIM1 exerts its role in cell population growth via different mechanisms, as demonstrated previously. Upon PIM1 knockdown, MDA-MB-231 showed lower motility persistence, increased circularity and a reduction of F-actin filaments. To understand the common downstream targets of PIM1 and SHP2 and elucidate the pathway by which PIM1 may control cell migration, we used phospho-kinase arrays. These revealed decreased phosphorylation of PI3K, AKT, and PYK2, proteins involved in cell migration, upon either PIM1 or SHP2 knockdown.

Conclusions: These data suggest that PIM1 regulates cell migration by controlling PTPN11/SHP2 expression and provide further evidence for PIM1 as a target for TNBC therapy, not only to induce apoptosis and prevent tumour growth, but also to prevent TNBC migration.

Legal entity responsible for the study: King’s College London/Breast Cancer Now Funding: Breast Cancer Now

Disclosure: All authors have declared no conflicts of interest.

**11P** SHP-1 agonist SC-43 enhanced the anti-tumor effect of docetaxel through suppressing p-STAT3 in triple negative breast cancer cells


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Background: Triple negative breast cancer (TNBC) is an aggressive cancer and its prognosis remains poor. Combinational therapies are a promising strategy for enhancing treatment efficacy. Blockade of STAT3 signaling have been shown to enhance the response of cancer cells to conventional chemotherapeutic agents. Here we used a SHP-1 agonist SC-43 to dephosphorylate STAT3, thereby suppressing oncogenic STAT3 signaling, and tested it in combination with docetaxel in TNBC cells.

Methods: TNBC cell lines (HCC-1937, MDA-MB-468, MDA-MB-231) were used for in vitro studies. Cell viability was assessed by MTT assay. Combination index was calculated for the migration of TNBC cells. We therefore studied whether PIM1 was also associated to this phenotype in TNBC cell lines. PIM1 knockdown led to a defect on 2D-transwell migration in MDA-MB-231 and SUM159 cells, similar to that observed upon SHP2 knockdown. Interestingly, SHP2 knockdown did not affect short-term cell population growth of TNBC cells, suggesting that PIM1 exerts its role in cell population growth via different mechanisms, as demonstrated previously. Upon PIM1 knockdown, MDA-MB-231 showed lower motility persistence, increased circularity and a reduction of F-actin filaments. To understand the common downstream targets of PIM1 and SHP2 and elucidate the pathway by which PIM1 may control cell migration, we used phospho-kinase arrays. These revealed decreased phosphorylation of PI3K, AKT, and PYK2, proteins involved in cell migration, upon either PIM1 or SHP2 knockdown.

Conclusions: These data suggest that PIM1 regulates cell migration by controlling PTPN11/SHP2 expression and provide further evidence for PIM1 as a target for TNBC therapy, not only to induce apoptosis and prevent tumour growth, but also to prevent TNBC migration.

Legal entity responsible for the study: King’s College London/Breast Cancer Now Funding: Breast Cancer Now

Disclosure: All authors have declared no conflicts of interest.
Methods: We used two-cell lines to investigate possible mechanisms of primary and secondary resistance to T in HER2+ and hormone receptor negative BC. AU565 sensitive to T (AU565-S), and HCC1954 as a primary T-resistant cell line. A third cell line with acquired resistance to T (AU565-R) was generated by treating AU565-S cells with constant dose of T (15mg/mL) for 4 months. Cell viability was estimated by MTT assay. We explored the expression of AXL by Western blot (WB) and quantitative reverse transcriptase PCR (qRT-PCR).

Results: The cell viability analysis at 7 days assay confirmed AU565-S as sensitive to T. HCC1954 as primary resistant and the development of a secondary resistance to T (AU565-R) (50% of increased viability from AU565-S). HER2 overexpression in all three cell lines were confirmed by WB and FISH. qRT-PCR indicated an important up-regulation of AXL at mRNA levels in AU565-R and HCC1954 compared to AU565-S (p < 0.05). In the same line, WB analyses showed a significantly increase in AXL protein expression in AU565-R and HCC1954 (2.03 and 3.97 fold, respectively). Finally, a selective AXL inhibitor (TP-0903) has demonstrated reduction of viability in all cell lines and significant restoration of sensitivity to T in AU565-R (p < 0.01).

Conclusions: Our results suggest: 1) AXL could be a potential mechanism of both primary and secondary resistance to T; 2) combination therapy with AXL inhibitor plus T restored T sensitivity in in vitro model with AXL overexpressed. These results merit further study and to explore this RTK as possible therapeutic targets in case of anti-HER2 treatment failure.

Legal entity responsible for the study: Clinic Hospital Universitario de Valencia. Biomedical Research Institute INCLIVA

Funding: None

Disclosure: I. Perez Fidalgo: Received fees from AstraZeneca, Ipsen, Novartis, Pfizer and Roche for participation in speaker bureaus. Had travel/accommodation expenses paid/reimbursed by AstraZeneca, Roche and Sanofi. All other authors have declared no conflicts of interest.

Alterations to trastuzumab-induced antibody-dependent cell-mediated cytotoxicity (T-ADCC) in a lapatinib-resistant HER2+ breast cancer cell line model

Methods: We used two-cell line to investigate possible mechanisms of primary and secondary resistance to T in HER2+ and hormone receptor negative BC. AU565 sensitive to T (AU565-S), and HCC1954 as a primary T-resistant cell line. A third cell line with acquired resistance to T (AU565-R) was generated by treating AU565-S cells with constant dose of T (15mg/mL) for 4 months. Cell viability was estimated by MTT assay. We explored the expression of AXL by Western blot (WB) and quantitative reverse transcriptase PCR (qRT-PCR).

Results: The cell viability analysis at 7 days assay confirmed AU565-S as sensitive to T. HCC1954 as primary resistant and the development of a secondary resistance to T (AU565-R) (50% of increased viability from AU565-S). HER2 overexpression in all three cell lines were confirmed by WB and FISH. qRT-PCR indicated an important up-regulation of AXL at mRNA levels in AU565-R and HCC1954 compared to AU565-S (p < 0.05). In the same line, WB analyses showed a significantly increase in AXL protein expression in AU565-R and HCC1954 (2.03 and 3.97 fold, respectively). Finally, a selective AXL inhibitor (TP-0903) has demonstrated reduction of viability in all cell lines and significant restoration of sensitivity to T in AU565-R (p < 0.01).

Conclusions: Our results suggest: 1) AXL could be a potential mechanism of both primary and secondary resistance to T; 2) combination therapy with AXL inhibitor plus T restored T sensitivity in in vitro model with AXL overexpressed. These results merit further study and to explore this RTK as possible therapeutic targets in case of anti-HER2 treatment failure.

Legal entity responsible for the study: Clinic Hospital Universitario de Valencia. Biomedical Research Institute INCLIVA

Funding: None

Disclosure: I. Perez Fidalgo: Received fees from AstraZeneca, Ipsen, Novartis, Pfizer and Roche for participation in speaker bureaus. Had travel/accommodation expenses paid/reimbursed by AstraZeneca, Roche and Sanofi. All other authors have declared no conflicts of interest.

Delineating the mechanisms of resistance to panHER inhibitors in HER2+ breast cancer cells

Methods: The expression of EGFR and BCL-2 protein family members was determined by immunoblotting and qPCR. CellTiter-Glo was used to measure cell viability and AnnexinV/PI staining and flow cytometer was used to evaluate apoptotic response. BH3 profiling was used to determine the apoptotic blocks and mitochondrial cell death pathway in primary breast cancer cells.

Results: Here we showed that increased MCL-1 and decreased BIM mediated resistance to neratinib in ZR-75-30 and SKBR3 cells while increased BCL-2 and BCL-2 decreased MCL-1 and increased BIM presented neratinib resistance in BT474 cells. Cells were also cross-resistant to dacomitinib. BH3 profiling in BT474 showed that BH3 profile of MCL-1 and BIM were increased in BT474 cells. BH3 profiles of HER2+ breast cancer efficiently predicted anti-apoptotic protein dependence and development of resistance to panHER2 inhibitors. Adding specific ERK1/2 inhibitor SCH 772984 to neratinib or dacomitinib led to increased apoptotic response in SKBR3 and ZR-75-30 cells, but did not inhibit reactivation of ERK1/2 in BT474 cells. Reactivation of ERK1/2 was preferentially related to acquired resistance in SKBR3 and ZR-75-30 cells. Intriguingly, both ERK1/2 and Akt/NF-kappaB pathways were responsible for resistance in BT474 cells.

Conclusions: Our results showed that different mitochondrial apoptotic blocks mediated acquired panHER2 resistance in HER2+ breast cancer cells as well as highlighted the potential of BH3 profiling assay in prediction of panHER2 resistance in breast cancer cells.

Legal entity responsible for the study: Ozgur Kutuk

Funding: Baskent University

Disclosure: All authors have declared no conflicts of interest.
Estrogen-dependent breast cancer: The importance of androgen receptor in exemestane treatment

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**Background:** Exemestane (Exe) is a third-generation steroidal aromatase inhibitor (AI) that is a standard therapeutic approach for post-menopausal women with estrogen-receptor positive (ER+) breast cancer. Besides its clinical benefit, acquired resistance may develop. Thus, to avoid this drawback it is urgent to find new targets that can improve breast cancer treatment. It is known that 85–95% of the ER+ breast cancers, overexpress androgen receptor (AR), that has a dual function in breast cancer development, depending on hormonal cell status. It has been described that in AI-sensitive breast cancer cells this receptor promotes cell death. Several clinical trials are ongoing to study the efficacy of combining AR antagonists, as bicalutamide (CDX), with Exe, but the benefit of targeting AR is not well defined. In that way, this work will investigate the biological significance of AR in Exe-treated breast cancer cells and the effectiveness of targeting AR.

**Methods:** In ER+ breast cancer cells that overexpress aromatase (MCF-7/Aro), it was investigated in the vitro effects of the AR antagonist CDX in Exe-treated cells. The cell impact was studied in viability and proliferation using MTT assay and flow cytometry, respectively. The cell cycle was evaluated for caspase activity. The expression/activation of AR and the effects on PI3K and MAPK pathways were studied by Western-blot.

**Results:** Exe induces an overexpression and hyperactivation of AR in MCF-7/Aro cells. By blocking AR with CDX, it was observed an increase in the reduction of viability and proliferation of Exe-treated cells, when comparing to Exe alone. An increase in caspase-8, -9, -7 and -6 was also observed for the combination. In addition, CDX inhibits the Exe-induced activation of cell proliferation/survival MAPK pathway and caused no effect on PI3K pathway.

**Conclusions:** This study suggests that, contrary what is described for other AIs, the AR as a pro-survival role in sensitive breast cancer cells treated with Exe and that by targeting AR it is possible to improve the clinical efficacy of Exe, by inhibiting cell proliferation and inducing apoptosis. This work contributes to the understanding of the link between AR and Exe and will highlight new targets to improve breast cancer treatment.

Legal entity responsible for the study: UCIBIO, REQUIMTE, Faculty of Pharmacy, University of Porto.

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**Disclosure:** All authors have declared no conflicts of interest.

Phosphatidylinositol 3-kinase (PI3K)/Akt axis blockade with taselisib or ipatasertib enhances the efficacy of anti-microtubule drugs in human breast cancer cells

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**Background:** The phosphatidylinositol 3-kinase (PI3K) pathway is commonly altered in breast cancer patients, but its role is still unclear. Taselisib, a mutant PI3K/CDC2K inhibitor, and ipatasertib, an AKT inhibitor, are currently under investigation in clinical trials in combination with paclitaxel or hormonal therapies in breast cancer. The aim of this study was to evaluate if PI3K or AKT inhibition can prevent resistance to chemotherapy and potentiate its efficacy.

**Methods:** The efficacy of combined treatment of taselisib or ipatasertib plus vinorelbine or paclitaxel or eribulin was evaluated in vitro on human breast cancer cells (with different expression profile of hormonal receptors, HER2, and of PI3Kα mutation) on cell survival, proliferation. The MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) and on cell apoptosis by flow-cytometry analysis. We also investigated the effect of combined treatment on downstream intracellular signaling, by western blot analysis, and on metastatic properties, by migration assays. Finally, we analyzed changes in cell cytokines by immunofluorescence.

**Results:** A significant synergism of ipatasertib or taselisib plus anti-microtubule chemotherapy in terms of anti-proliferative, pro-apoptotic and anti-metastatic effect was observed. The combined treatment completely inhibited the activation of proteins downstream of PI3K and MAPK pathways and affected the expression of survivin. Combined treatments completely disorganized the cytokines in human breast cancer cells, thus suggesting a potential mechanism for this combination.

**Conclusions:** Targeting PI3K may enhance the efficacy of anti-microtubule drugs in human breast cancer.
TNF-α did. The MDA-TSFs were able to increase the HUVEC monolayer permeability exceeded about 30% of the TNF-α induced permeability. A 1.5-fold increase of transendothelial migration cells was observed in HUVEC stimulated with MDA-MB-231 TSFs.

Conclusions: Tumor secreted factors derived from highly metastatic cell line MDA-MB-231 are capable to induce a premetastasis-like endothelial state, increasing the tumor cell transendothelial migration, adhesion to the HUVEC monolayer as well as vascular permeability enhancement.

Clinical trial identification: 11-62-2014

Legal entity responsible for the study: Instituto de Investigaciones Biomédicas, UNAM

Funding: Programa de Doctorado en Ciencias Biomédicas, Universidad Nacional Autónoma de México (UNAM), fellowship 509589 from CONACYT.

Disclosure: All authors have declared no conflicts of interest.

20P Selective accumulation of the rat adherent natural killer cells in mammary tumor tissues

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Background: In the present study, we attempted to clarify what kind of adhesion molecules and tumor cytototoxic killer activity A-NK cells can express, when cultured for long period and then tried experimentally to augment the selective accumulation the A-NK cells into rat mammary tumors, in combination with the prior injection of various kinds of adjuvants into the tumor region. The mechanisms by which the effect of cells accumulate in tumor tissue will be discussed.

Methods: 1. Animals: Specific pathogen-free (SPE) female rats. 2. Preparation of A-NK cells: A-NK cells were isolated from spleenic lymphocytes. 3. Antibodies: Monoclonal antibodies, and Anti adhesion molecule antibodies. 4. Immunohistochemical staining and Flow cytometric analysis. 5. Preparation of mammary tumour bearing rats.

Results: Immunocytochemical and flow-cytometric analysis revealed that most of the A-NK cells strongly expressed lymphocyte function-associated antigen 1 throughout the incubation. All A-NK cells from 8-150 day cultures, particularly those cultured for 8 days, showed significant cytotoxic activity against all targets. Peritumoral injection of various kinds of adjuvant, particularly Freund’s complete adjuvant plus bacillus Calmette-Guerin, resulted in a marked accumulation of A-NK cells in mammary tumor tissues 24 h after injection, and simultaneously in the formation of vessels resembling high-endothelium venules, and expression of the ICAM-1 molecule on the tumor cells in the sites of tumor tissues. When A-NK cells were intravenously administered, significant retardation of tumor growth and prolongation of survival of tumor-bearing rats were observed in the groups that received the prior injection of adjuvants.

Conclusions: These results indicate that the prior injection of proper adjuvant into the peritumoral region is effective for the selective accumulation or infiltration of A-NK cells into the sites of tumor tissues, and results in the marked retardation of tumor growth.

Legal entity responsible for the study: School of Rehabilitation Sciences

Funding: None

Disclosure: The author has declared no conflicts of interest.

21P Inhibition of nitric oxide synthase (NOS) reduces the effect of stress hormone signalling in breast cancer

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Background: Expression of nitric oxide synthase (NOS) has been found to correlate with tumour progression in breast cancer, indicating that NO activity may drive malignant growth. Previously we have shown that the stress hormone cortisol acts through a nitric oxide synthase (NOS) mediated pathway to induce production of nitric oxide (NO), and can induce DNA damage in breast cancer.

Methods: Breast cancer cell lines MCF-7 and MDA-MB-231 as well as the mouse mammary tumour cell line 66CL4 were exposed to cortisol and levels of intracellular NO, and can induce DNA damage in breast cancer.

Results: Inhibition of nitric oxide synthase (NOS) has been found to correlate with tumour progression in breast cancer, indicating that NO activity may drive malignant growth. Previously we have shown that the stress hormone cortisol acts through a nitric oxide synthase (NOS) mediated pathway to induce production of nitric oxide (NO), and can induce DNA damage in breast cancer.

Conclusions: We demonstrated that L-NAME, through inhibition of NO signalling, is effective in reducing primary tumour formation and metastatic potential in stressed mice. This data may have impact for patients with breast cancer experiencing extreme stress and further genomic analysis are ongoing.

Legal entity responsible for the study: School of Pharmacy and Biomolecular Sciences, University of Brighton, UK

Funding: Rising star initiative, University of Brighton.

Disclosure: All authors have declared no conflicts of interest.

22P The interplay between TP53 and mevalonate pathway in ovarian cancer

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Background: TP53 gene is the most commonly mutated tumor suppressor in human malignancies. TP53 is mutated in more than 50% of all human cancers, with over 90% of high-grade serous ovarian cancer displaying changes at this locus. Mutations of TP53 gene is associated with malignant transformation and resistance to chemotherapy. In addition, previous studies have shown that ectopic expression of TP53 mutant form in breast cancer cells leads to increased transcription of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGR). This enzyme regulates the synthesis of geranyl-geranol which is used to post-translationally modify small G-T-Pase oncogenes. HMGR is itself considered to be a metabolic oncogene. Stains, which inhibit HMGR, are potential cancer therapeutic agents that can cause ovarian cancer (OC) cell apoptosis and regression of xenografts.

Methods: The level of mevalonate pathway (MP) enzymes evaluated in panel of OC cell lines using immunoblotting. In addition, MP enzymes were expressed using qPCR following ectopic expression of wild-type and R248W, R175H, and R273H p53 variants in Skov-3 cells and after inhibition of TP53 expression using siRNA directed to TP53 mRNA in Ovar-3 cells.

Results: We confirmed that the expression of HMGR is higher in OC cell lines than in normal epithelial ovarian cells. The level of geranylgeranyl transferase I-β (GGTI-β) and Geranylgeranyl transferase II-β (GGTI-β) was significantly increased in Skov-3 cells, which lack endogenous p53 protein, led to significantly increased expression of HMGR, GGTI-β, and Farnesyltransferase-β (FT-β) enzymes compared to cells transfected with vector. The inhibition of the pre-existing mutations in TP53 encoding R248Q in Ovar-3 cell lines. The ectopic expression of TP53 variants in Skov-3 cells, which lack endogenous p53 protein, led to significantly increased expression of HMGR, GGTI-β, and Farnesyltransferase-β (FT-β) enzymes compared to cells transfected with vector. The inhibition of the pre-existing mutations in TP53 encoding R248Q in Ovar-3 cell lines significantly decreased p53 protein and also HMGR, GGTI-β, and FT-β mRNA.

Conclusions: These data suggest that TP53 mutations play critical role in regulation of the activity of MP enzymes, providing a rationale for the evaluation of the pathway inhibitors such as statins and bhosphonates in the treatment of OC.

Legal entity responsible for the study: The study was designed by AR and MIA, the experimental work was conducted by MIA and MNA.

Funding: Higher Committee for Education Development in Iraq (MIA ref D-11-296).

Disclosure: All authors have declared no conflicts of interest.

23P Epigenomic landscape of breast cancer in very young women

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Background: Although less frequent than in older women, breast cancer in very young women (BCVY) (<35 years old) presents more aggressive and complex biological features. Epigenetic modifications such as miRNA regulation or DNA methylation are reported to play an important role in the onset and progression of cancer. The aim of this work is to identify the epigenetics mechanisms characteristics of BCVY that may be conferring more aggressive features to this group of patients.

Methods: We analysed methylation (Infinium MethylationEPIC BeadChip) from 26 BCVY and 15 samples from women > 45 years old. Methylation differences were assessed using Wilcoxon rank sum test. We selected from The Cancer Genome Atlas (TCGA) those genes regulated by significantly different methylated sites and their expression was analysed. miRNA expression data from TCGA, METABRIC and data previously published from our group was evaluated in a meta-analysis. We then selected those target genes which expression was more affected by miRNA deregulation.

Pathway enrichment analysis was performed with most relevant genes from the epigenetic study by Enrichr.

Results: We detected a global hypomethylation profile in BCVY samples and hypermethylation of 302 specific CpG sites exclusive of this group of age. Hypomethylated CpG sites were regulatory sites mainly involve in neuronal processes, extracellular matrix and cell communication. Whereas specific hypomethylation was located in genes related to immune system, NOTCH signalling, vesicular trafficking, DNA repair and senescence. miRNA expression meta-analysis revealed a profile of 22 miRNAs significantly deregulated in BCVY. Pathway enrichment analysis of most affected target genes showed an involvement in neural processes, glucose metabolism, vesicular trafficking,
DNA repair, histone and chromatin related proteins, apoptosis, cell cycle, response to DNA damage and senescence.

Conclusions: Our work highlights the presence of epigenomic profile distinctive of BCVY. Both methylation and miRNAs studies points to deregulation of pathways related to neural processes, vesicular trafficking, DNA repair and senescence. Some of these processes may lead to cancer development and progression, thus genes in these pathways may be potential candidates for further studies.

Legal entity responsible for the study: INCLIVA Research Institute
Funding: None
Disclosure: S. Sanchis: Funded on a FPU predoctoral Fellowship (FP13/04976) from MINECO, Spanish Government.

G. Ribas: Funded on a Miquel Serveit II contract (CPII14-00013) from CarlosIII Health Institute.

M.P. Chilet: Funded by private Patients Foundation LeCado. CIBERONC is an initiative of the Carlos III Health Institute. All other authors have declared no conflicts of interest.

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# Evaluation of cell free circulating DNA in plasma by digital PCR for early diagnosis in Peruvian breast cancer patients

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Background: New diagnostic tools can be useful and give clinical benefits, including diagnosis, prognosis, treatment and monitoring of the disease. A non-invasive method is the study of liquid biopsies, performed in fluids containing cell-free circulating DNA (cfDNA). Analyses with digital PCR technique (dPCR) allows to establish the levels of cfDNA as well as the absolute quantification of mutants alleles with accuracy. This system scatters the sample among twenty thousand wells (microfluods on the chip), where amplification reactions occur independently and are recorded by a reader.

Methods: Peripheral blood samples were obtained from breast cancer patients and healthy controls. From each sample, the cDNAs were extracted from plasma using the MagMAX™ Cell Free DNA Isolation Kit and dPCR was done for quantification of Peripheral blood samples were obtained from breast cancer patients and controls, cell free DNA is a good biomarker that can be used in the diagnostic of breast cancer. On the other hand, digital PCR has been established as a good tool to check cfDNA levels from plasma of breast cancer patients.

Results:

- Significant differences were found in the values of cfDNA between patients and controls for PUM1 (p = 0.0001) and RNaseP (p = 0.0003). These results allowed to establish cut-off points between groups at 78.995 and 51.154 copies/μl, respectively.
- These values can be considered in the classification of groups for further analysis of others samples. Statistical support for the use of markers in diagnosis was also evaluated using the ROC curve that favors the PUM1 marker, with a sensitivity of 75% and a specificity of 95.2%.

Conclusions: Based on the signficant differences found between breast cancer patients and controls, cell free DNA is a good biomarker that can be used in the diagnostic of breast cancer. On the other hand, digital PCR has been established as a good tool to check cfDNA levels from plasma of breast cancer patients.

Legal entity responsible for the study: Jose Buley

Funding: Programa Nacional para la competitividad y Productividad (Innovate Peru)-No.138-PRICIP-PPAP-2015, Universidad de San Martin de Porres, Oncosalud - AUNA

Disclosure: All authors have declared no conflicts of interest.

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# Breast cancer predisposing germline mutations identified by exome sequencing

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Background: A significant portion of hereditary predisposition to breast cancer (BC) is attributed to yet unknown factors. Russian population is characterized by surprisingly strong founder effect, therefore whole exome sequencing (WES) for a limited number of these genetically homogenous patients has a potential to identify novel BC-predisposing genes.

Methods: WES was performed for 32 Russian BC cases, which demonstrated strong clinical signs of the hereditary disease (family history, BC bilaterality, young onset) and lacked germline mutations in “canonical” BC genes (BRCA1, BRCA2, CHEK2, PALB2, and NBS1/BRCA1).


Conclusions: This study revealed several alleles, which may be associated with increased BC predisposition. However, in contrast to well-known Slavic BRCA founder mutations, newly identified candidates are exceptionally rare and therefore are unlikely to be suitable for a significant share of BC morbidity. Supported by the RSF grant No 16-45-00211.

Legal entity responsible for the study: Evgeny N. Imyanitov, Head of the Department of Tumor Biology in the N.N. Petrov Institute of Oncology.

Funding: Russian Scientific Fund (grant No 16-45-00211).

Disclosure: All authors have declared no conflicts of interest.

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# Global transcriptome deregulation of breast cancer in very young women samples

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Background: Breast cancer in young women (under 35 years) (BCVY) often presents distinct clinic-pathological features: more aggressive phenotype and worse prognosis than older women. Genomic and molecular alterations play a significant role in breast cancer biology. Due to the low incidence of BCVY (2-5%) these women are underrepresented in most molecular studies. This work presents a comprehensive study of the transcriptome in BCVY, focusing in the search of gene expression biomarkers characteristic of this group of patients.

Methods: We analysed the transcriptome by Clariom™ D (Affymetrix) from 31 BCVY and 11 samples from women >45 years old. Global gene expression was filtered and normalized by RMA method. After initial pre-processing we analysed expression in 3,639 mRNAs, 66,457 lncRNA and 3,271 pre-miRNA and differences were assessed after meta-analysis with TCGA gene expression data and own data, 43 genes presented in most molecular studies. This work presents a comprehensive study of the transcriptome in BCVY, focusing in the search of gene expression biomarkers characteristic of this group of patients.

Results: Fourteen genes were enriched in BCVY compared with older women. Genomic and molecular alterations play a significant role in breast cancer biology. Due to the low incidence of BCVY (2-5%) these women are underrepresented in most molecular studies. This work presents a comprehensive study of the transcriptome in BCVY, focusing in the search of gene expression biomarkers characteristic of this group of patients.

Conclusions: This study was performed and published in 2015.

Legal entity responsible for the study: None

Disclosure: All authors have declared no conflicts of interest.

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# Breast cancer in very young women: differences in expression of genes implicated in DNA repair, histone and chromatin related proteins, apoptosis, cell cycle, response to DNA damage and senescence

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Background: Breast cancer in young women (under 35 years) (BCVY) often presents distinct clinic-pathological features: more aggressive phenotype and worse prognosis than older women. Genomic and molecular alterations play a significant role in breast cancer biology. Due to the low incidence of BCVY (2-5%) these women are underrepresented in most molecular studies.

Methods: We analysed the transcriptome by Clariom™ D (Affymetrix) from 31 BCVY and 11 samples from women >45 years old. Global gene expression was filtered and normalized by RMA method. After initial pre-processing we analysed expression in 3,639 mRNAs, 66,457 lncRNA and 3,271 pre-miRNA and differences were assessed using t-test. We performed a meta-analysis with gene expression data from The Cancer Genome Atlas (TCGA) for validation of results. Pathway enrichment analysis was performed by Enrichr.

Results: We showed a specific transcriptomic landscape in BCVY. Clariom D study revealed 134 significant mRNA with p-value <0.05 that pointed out pathways related to olfactory receptors, GPCR signalling, tight junction and cell-cell communication. After meta-analysis with TCGA gene expression data and own data, 43 genes were statistically significant and 15 of those with high FDR correction (FDR < 0.05). Among those we found PIK3CB, HOXD10, NBN364, TMEM204, IRX5, IF4, MAGEA2 and TSR2 deregulated in BCVY compared with older women. Pathway enrichment analyses and GO search highlight pathways related to cell-cell communication, cancer processes, chemokine and PDK signalling pathways, cell differentiation, extracellular matrix, vesicular trafficking, neuronal processes among others.

Conclusions: We find the presence of a distinctive transcriptomic profile of the BCVY samples. Our study points to deregulation of pathways related to cell migration, proliferation and differentiation that promote cancer development and progression. Genes obtained in meta-analysis might be potential target genes for further studies in BCVY which could help to clarify the biological background for the development of the disease in this group of age.

Legal entity responsible for the study: INCLIVA Instituto de investigación

Funding: None

Disclosure: S. Sanchis: Funded on a FPU predoctoral Fellowship (FP13/04976) from MINECO, Spanish Government. G. Ribas: Funded on a Miquel Serveit II contract (CPII14-00013) from CarlosIII Health Institute. M.P. Chilet: Funded by private Patients Foundation LeCado. CIBERONC is an initiative of the Carlos III Health Institute. All other authors have declared no conflicts of interest.
Results: The identified genes not only included select genes previously linked to PC, such as members of the topoisomerase and cyclin families, but also novel genes that had not been observed in enzalutamide-resistant tumours. The identified gene-signature and expression correlated with patients' Gleason score and had a prognostic value that predicted disease progression at the time of patient biopsy in large independent cohorts.

Conclusions: This comprehensive and clinically relevant approach will allow complete elucidation of the role of ELF3 in normal prostate development and to explore its role in PCa. This approach will also provide a novel mechanism of resistance to the anti-androgen Enzalutamide. Other non-AR dependent mechanisms of resistance have also emerged including acquisition of a hypoxic microenvironment. We propose treatment-induced hypoxia and the induction of angiogenesis may define a novel mechanism of resistance to Enzalutamide.

Methods: Preclinical experiments were conducted in LNCaP tumours and established human prostate cancer cell lines. Tumour growth, intra-tumoral hypoxia and blood vessel density were measured in vivo. AR expression, activation and target gene expression were measured in vitro. Effects of Enzalutamide on hypoxia-driven, disease-progressing pathways and genes of interest and the role of these genes in resistance to Enzalutamide was investigated.

Results: Enzalutamide promoted persistent hypoxia in LNCaP tumours in vivo, followed by increased blood vessel density and restoration of oxygen tension (>14 days). In vitro, hypoxia increased AR expression and transcriptional activity in LNCaP cells and sustained but did not further potentiate high basal AR and ARv7 activity in 22Rv1 cells. Enzalutamide failed to attenuate the concurrent hypoxia-induced HIF-1 and NF-κB signalling, resulting in up-regulation of disease-progressing genes and pathways. Administration of neutralizing antibodies to two hypoxia regulated genes, IL-8 and VEGF prolonged Enzalutamide-mediated LNCaP tumour growth control over 28 days in vivo (p < 0.001) and re-sensitised enzalutamide-resistant LNCaP cells in vitro.

Conclusions: Enzalutamide-induced hypoxia upregulates the expression of VEGF and IL-8, whose multi-model signalling effects contribute to microenvironment-promoted resistance in prostate tumours.

Legal entity responsible for the study: David Waugh.

Funding: Prostate Cancer UK.

Disclosures: R. Oksala, M. Karimaa, M. Ramela, R. Riiokonen, P. Rummakko, G. Wohlfahrt, A. Vuorela, M.V. Mustonen, P. Kallio: Employee: Orion Corporation Orion Pharma. All other authors have declared no conflicts of interest.

Prostate Cancer UK (PCUK) registered charity.

Disclosure: All authors have declared no conflicts of interest.

30P Treatment-induced hypoxia attenuates enzalutamide response and promotes resistance in pre-clinical models of prostate cancer

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Disclosure: All authors have declared no conflicts of interest.

Background: Androgen receptor (AR) plays a central role in prostate cancer and continues to be a driver in castration-resistant prostate cancer (CRPC), with increased AR expression in most cases. Approximately half of the men with CRPC respond initially to abiraterone or enzalutamide, but most relapse within 1-2 years. Majority of the abiraterone and enzalutamide-resistant tumours have high AR expression and persistent AR activity. Several precursor steroids, like testosterone (T) and dihydrotestosterone activate AR, are synthesized in adrenal glands and de novo in tumours. CYP11A1 (cholesterol side-chain cleavage enzyme) is a mitochondrial enzyme catalysing the conversion of cholesterol to pregnenolone (Preg), which is the first rate-limiting step in steroid hormone biosynthesis. ODM-208 is a novel, oral, non-steroidal and selective inhibitor of CYP11A1 enzyme and suppresses the synthesis of all steroid hormones and precursors.

Methods: The inhibition of CYP11A1 was measured in vitro by detecting the formation of radio labelled isocaproic acid in a human adrenal cortex cell line (H295R), and further analysing Preg and T formation by ELISA. Inhibition of the adrenal and testicular hormone production in vivo was tested in the intact male rat assay by analysing plasma concentrations of progestosterone (P), corticosterone (C) and T (with LS-MS/MS) after single oral dose of ODM-208. The tumour growth inhibition was studied by using androgen dependent VCaP cells, which were subcutaneously grafted to intact male nude mice. When tumour volumes reached on average 200 mm3, mice were castrated, and after regrowth of the tumours, the oral treatment of ODM-208 was started.

Results: ODM-208 potently inhibits CYP11A1 enzyme and formation of Preg and testosterone with low nM concentrations in vitro. In male rats, clear decreases of P, C and T concentrations can be detected already after single oral administration of ODM-208. In the murine VCaP CRPC xenograft model ODM-208 significantly inhibited tumour growth.

Conclusions: ODM-208 shows promising antitumor activity in preclinical CRPC models and suggests that ODM-208 may have the potential to be an effective treatment in CRPC. Clinical trial in patients with metastatic CRPC is planned to be started in the 2018.

Legal entity responsible for the study: Orion Corporation Orion Pharma.

Funding: Orion Corporation Orion Pharma.
Background: Cell-free DNA (cfDNA) has been known to be released from tumor cells and used as potential biomarkers for therapeutic responses. However, the role of cfDNA in pancreatic cancer has not been well studied. Here we selected KRAS mutation which has been known common over 95% of pancreatic ductal adenocarcinoma (PDA) and evaluated applicability as a prognostic marker through the quantitative analysis of cfDNA and KRAS mutation in the patients with PDA.

Methods: Total of 106 PDA patients were enrolled in the study. The concentration and fraction of KRAS mutation were measured by KRAS screening multiplex droplet digital PCR kit (Biorad, USA) in plasma samples.

Results: KRAS mutation was detected in 97.4% of tissue samples and the correlation with cfDNA was 0.61 with 80.5% positivity. KRAS mutation concentration and fractional abundance showed the association with poor survival in both PFS (P = 0.001 and P = 0.001) and OS (P = 0.003 and P = 0.006) in the entire stage groups. Stage-specific, the impact for survival of KRAS mutation concentration and fractional abundance was obvious in PFS in resectable group (P = 0.016 and P = 0.012). When we analyzed the receiver operating characteristic (ROC) curve to characterize whether KRAS mutation in cfDNA have additive benefits with well-known tumor markers CA19-9, combined with KRAS mutation status or KRAS fractional abundance, the value of area under the curve (AUC) was significantly higher than the value calculated as CA19-9 alone.

Conclusions: This study represents that KRAS mutation concentration and fractional abundance in cfDNA could be prognostic marker in pancreatic cancer especially in resectable group.

Legal entity responsible for the study: Sun-Young Kong

Disclosure: This work was supported by grants from the National Cancer Center of Korea (NCC-1510203).

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Title: Prognostic Impact of KRAS Mutation in Cell-Free DNA in Patients with Pancreatic Cancer


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33P

Synergistic effect of vismodegib and cisplatin in NSCLC models via autophagy

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Background: Platinum-based chemotherapy still represents the standard first-line approach for NSCLC patients, although primary or secondary resistance is frequently observed. Recently the Shh pathway has been associated with resistance to platinum-based chemotherapy in NSCLC. The aim of this work is to investigate whether a combined treatment with cisplatin and the Hedgehog-pathway inhibitor vismodegib could potentiate the anti-tumour effect and to explore possible mechanisms of this synergy.

Methods: Two Human NSCLC cell lines A549 and H460 were treated with single agent Cisplatin, single agent Vismodegib and a combination of the two drugs. MTTR cytotoxicity assays were performed and the data were analysed with Compusyn software. Experiments of apoptosis and cell cycle were done by using flow cytometer. Immunofluorescence with lypoTracker as well as western blot (WB) analysis for the LC3 protein were performed to analyse autophagy.

Results: The Compusyn analysis showed an improved synergistic effect of cisplatin + Vismodegib. Combined treatment induced a significant increase in cellular apoptosis compared with single agent cisplatin. The cell cycle analyses revealed a block in S-phase with the combination treatment. The lypoTracker immunofluorescence assay showed that cisplatin induces an increase of autophagy, while the combination with vismodegib strongly reduces it, finally reverting this effect. These findings were confirmed by WB analysis for LC3B which is significantly increased by single agent cisplatin and reduced by the combined treatment.

Conclusions: Combined treatment with cisplatin and vismodegib has a synergistic effect with an increase in cancer cell apoptosis. Autophagy has been described as a mechanism through which cancer cells escape cisplatin-induced cytotoxicity. Combining cisplatin with vismodegib leads to an inhibition of autophagy, so that it could suggest a new therapeutic approach.

Legal entity responsible for the study: Università della Campania “Luigi Vanvitelli”

Disclosure: All authors have declared no conflicts of interest.

References:


32P

Isomorphic functions in pancreatic adenocarcinoma


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Background: AKT/PKB is a protein kinase that plays a key role in cancer, which is expressed as 3 isoforms: AKT1 (PKBα), AKT2 (PKBβ) and AKT3 (PKBγ). Although these isoforms are remarkably similar, there is evidence that each isoform yields specific functions which may vary depending on the cell type. Even so, the underlying molecular pathways specifically regulated by each one of them are unknown.

Methods: To gain insight into the role of each isoform in the biology of human pancreatic adenocarcinoma cells, we have silenced each AKT isoform individually using short hairpin RNA (shRNA). Humanized AD xenograft mouse models were inducible short hairpin RNA (shRNA). Humanized AD xenograft mouse models were inoculated with Id1 silenced H1792-604 cells (Id1 silenced or Id1 wild type) in banks of immunodeficient mice. Id1 silencing was activated at the time of tumor cell inoculation (chemoprevention assay) or once the tumors were established (therapeutic assay).

Results: Id1 inhibition was achieved in all selected cell lines compared to their controls. In vivo, in the chemoprevention assay we observed a significant decrease in tumor volume in mice injected with Id1 silenced H1792-604 cells (60% ± 32.39%) compared to the control group (356.29%± 115.32%) (P < 0.001). Moreover, mice inoculated with Id1 silenced H2009 cells never developed tumors compared to control mice (168.35 ± 68.71) (P < 0.001). In the therapeutic assay, the activation of inducible silencing of Id1 in established tumors induced a significant reduction of tumor volume in both xenograft models. Id1 inhibition induced a partial response in 60% of the tumors after injection of H1792-604 cells and in 100% of tumors in H2009 inoculated mice.

Conclusions: These findings encourage further evaluation of Id1 as a potential therapeutical target in KM NSCLC-AD patients.

Legal entity responsible for the study: Clínica Universidad de Navarra

Disclosure: All authors have declared no conflicts of interest.
A strong association between the rs4567312-LEPR polymorphism and lung cancer risk, all authors have declared no conflicts of interest.

Disclosure:

Funding:

Results:

Statistical comparison using two-way ANOVA identified 241 ratios (98 individual miRNAs) with significantly different expression between LC patients and HD (p < 0.05 after Benjamini-Hochberg correction). Using LASSO penalization models and manual filtering of miRNAs associated with haemorrhage, 7 miRNA ratios were identified as best predictors of cancer. Extended set of miRNAs (n = 19) was selected for further verification in an independent sample of 30 LC patients, 20 HD and 10 patients with hyper- and metaplastic endobronchitis using custom miCURY LNA miRNA qPCR Pick & Mix Panel.

Conclusions:

Based on expression in both data sets 5 ratios containing 7 miRNAs were selected for further validation in an extended cohort of LC and cancer-free individuals.

Legal entity responsible for the study: Laboratory of Molecular Medicine, SB RAS Institute of Chemical Biology and Fundamental Medicine, Novosibirsk, Russian Federation

Funding: Study has been supported by Russian Foundation for Basic Research (RFBR, grant No. 14-04-01881), BOR grant VI.62.1.4, and Presidium of RAS research program ‘Molecular and Cellular Biology’. No. 6.1.

Disclosure: All authors have declared no conflicts of interest.

Background:

DNA methylation is an epigenetic determinant of gene expression. Cytosine Phosphate G (CpG) is a phase I xenobiotic metabolizing enzyme, glutathione S-transferase P1 (GSTP1) detoxifies metabolites and regulates cellular stress response and death. Methylation changes in these genes could play a role in the incidence of cancer. Our aims were to analyze DNA-methylation of selected Cpg islands in the CpIA1 and GSTP1 genes at baseline in subjects who had incident cancer and paired controls and to determine if DNA methylation in cancer patients changed from baseline to the time close to cancer diagnosis.

Methods:

We followed-up 1094 subjects (aged 47 ± 6 years) from the PREDIMED-Valladolid study prospectively from 2003 to 2014. Cancer incidence was a secondary outcome in this trial. DNA-methylation of the CpIA1 and GSTP1 genes and incidence of major cancers (lung, breast and colon) in the PREDIMED-Valladolid study.

Results:

We detected 12 new cases of lung cancer from 2003 to 2014 (1.1% cumulative incidence). Tobacco smoking was strongly associated with lung cancer incidence (91.7% of current or former smokers in lung cancer subjects vs 41.3% in the non-cancer participants (p < 0.001). In the whole population, prevalence of the rs4567312 polymorphism was: 95.5% CC, 4.4% CT and 0.1% TT. We also detected in the whole population an association between this polymorphism and plasma leptin concentrations, 26.9 ± 22.9 ng/mL in CC vs 18.4 ± 16.7 ng/mL in T carriers (p = 0.013). We found a strong association between the rs4567312-LEPR polymorphism and lung cancer risk, being higher in carriers of the T-allele. This association remained statistically significant (OR = 7.61; 95% CI: 1.74-33.37 for T-carriers vs CC) even after adjustment for gender, age, tobacco smoking, dietary intervention group (MedHet vs control diet) and leptin levels.

Conclusions: We have detected differences in DNA-methylation of selected CpG islands in the CpIA1 and GSTP1 genes at baseline in subjects who had incident cancer and paired controls and to determine if DNA methylation in cancer patients changed from baseline to the time close to cancer diagnosis.

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Background:

Lung cancer (LC) is causing more than 1.3 million deaths worldwide annually. Early detection of LC is critical for success but despite recent advancements in LC diagnostics most patients are still diagnosed at advanced stages of the disease. The situation is further complicated by high intratumour heterogeneity and general diversity of lung malignancies. Insights into cancer genetics have kindled interest in molecular cancer diagnostics. One of the lucrative sources of prospective LC biomarkers is cell-free circulating miRNAs. These small non-coding RNAs are frequently deregulated in LC. It is also known that miRNAs can travel in bodily fluids for extended periods of time, shielded from degradation by membrane vesicles or other biopolymers. Recently, specific subsets of miRNAs associated with tumor phenotypes and disease progression have been found circulating in blood of cancer patients and suggested as potential biomarkers for LC.

Methods:

In the present study, we have investigated the profiles of circulating miRNAs in blood plasma of LC patients and healthy individuals (HD) in order to identify potential markers for lung cancer diagnostics. Small RNAs were isolated from blood plasma of 20 LC patients and 10 healthy individuals (HD) using protocol reported earlier (Zaporozhchenko et al., Anal Biochem, 2015). Profiles of miRNA expression were obtained using miCURY LNA miRNA qPCR Panels Plasma/Serum (Exonux). Ratio based normalization was applied to all miRNA’s with call rate higher than 80%.

Results:

We analyzed 1094 participants (398 men, 696 women) recruited in the PREDIMED study an association between this polymorphism and plasma leptin concentrations. We followed-up 1094 subjects (aged: 67 ± 6 years) at baseline to 0.345 ± 0.046 close to cancer diagnosis.

Conclusions:

We have detected statistically significant changes in DNA methylation levels at baseline in the CpIA1 and GSTP1 genes between cancer cases and controls (P = 0.008 for the CpIA1 gene and P = 0.049 for the CpIA1 gene). We detected statistically significant changes in DNA methylation prospectively in cancer patients. DNA methylation at the CpIA1 gene was 0.020 ± 0.034 at baseline vs 0.016 ± 0.013 close to cancer diagnosis (P = 0.044). For the GSTP1 gene, methylation of the CpIA1 gene prospectively increased from 0.327 ± 0.046 at baseline to 0.345 ± 0.053 (P = 0.014) close to cancer diagnosis.

Conclusions: We have detected differences in DNA methylation of selected CpG Islands of the CpIA1 and GSTP1 genes at baseline in subjects who had incident cancer and paired controls and to determine if DNA methylation in cancer patients changed from baseline to the time close to cancer diagnosis. This suggests a dynamic influence of DNA methylation that could be modulated for prevention.

Clinical trial identification: Controlled-trials.com number ISRCTN35793693

Legal entity responsible for the study: Instituto de Salud Carlos III and University of Valencia

Funding: Instituto de Salud Carlos III

Disclosure: All authors have declared no conflicts of interest.

Background:

Two-step microarray analysis of cell-free miRNA in plasma of lung cancer patients.

Methods:

I. Zagorushchenko, E. Marobin, A. Panamaryova, E. Rykova, N. Chendryntseva, V. Marov, P. Ivanov

1Department of Laboratory Medicine, Institute of Chemical Biology and Fundamental Medicine SB RAS, Novosibirsk, Russian Federation. 2Department of Molecular Oncology and Immunology, Tumour Cancer Research Institute IMM, Tomsk, Russian Federation. 3Institute of Chemical Biology and Fundamental Medicine SB RAS, Novosibirsk, Russian Federation

Background:

Cancer cells require increased glucose supply to sustain proliferation. Cancer cells require increased glucose supply to sustain proliferation. Cancer cells require increased glucose supply to sustain proliferation. This up-regulation of glucose transporters by protein kinases in cancer cells.

Results:

Regulation of glucose transporters by protein kinases in cancer cells.

Funding: None

Disclosure: All authors have declared no conflicts of interest.
so that more transporters are inserted into the plasma membrane. Previous work from the host lab has identified the family of WNK protein kinases and shown that WNK1 can also phosphorylate TBC1D4 and promote GLUT translocation to the cell surface. Our objective is to understand the contribution of WNK1 to glucose uptake in colorectal cancer cells. Our objective is to understand the contribution of WNK1 to glucose uptake in colorectal cancer cells.

**Methods:** To characterize the role of WNK1, various colorectal cell lines were first cultured with different glucose concentrations. Levels of GLUT1 at the cell surface were compared under these conditions and the effect of depleting WNK1 expression by siRNA determined.

**Results:** For selected conditions, key cell cycle or apoptotic marker proteins were analyzed by Western blot and revealed higher apoptotic and cell-cycle arrested phenotypes in WNK1-depleted cells cultured in low glucose medium. In order to dissect key phosphorylation events involved in GLUT1 regulation, mass spectrometry analysis revealed that WNK1 phosphorylates TBC1D4 and the functionally related TBC1D1 at unique Serine residues.

**Conclusions:** Together, these studies will elucidate the molecular details regulating the translocation of glucose transporters in cancer cells and have the potential to identify novel therapeutic targets.

**Legal entity responsible for the study:** Peter Jordan

**Funding:** Fundação para a Ciência e Tecnologia BioSI - Biosystems and Integrative Sciences Institute.

**Disclosure:** All authors have declared no conflicts of interest.

**41P** Signal transduction pathways regulating alternative splicing of tumor-related RAC1b

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**Human Genetics Department, Instituto Nacional de Saúde Doutor Ricardo Jorge, Lisbon, Portugal**

**Background:** In colon cancer distinct genetic subtypes have been described, one of which involves overexpression of RAC1b, a variant generated by alternative splicing. Abrupt translocation is known to occur in cancer and can be caused by mutation in a gene or splicing factor but also represents a dynamic response to oncogene-induced cellular signaling and in this case it may be pharmacologically targeted. Here we explore how signaling pathways are involved in the deregulation of alternative RAC1b splicing in colorectal tumor cells.

**Methods:** HT29 colorectal cells represent serrated colorectal tumors with BRAF gene mutation V600E in one allele and RAC1b overexpression. Cells were transfected with shRNA vectors directed against target candidate protein kinase transcripts and their effects on RAC1b levels analyzed 24h later by Western Blot and qRT-PCR. Treatment with kinase inhibitors or anti-inflammatory drugs was performed 24h prior to cell lysis.

**Results:** Two kinases, SRPK1 and GSK3b, were found to require sustained RAC1b levels and both were shown to act upon the phosphorylation of splicing factor SSRF1, which binds to and promotes the inclusion of the alternative exon in RAC1b. SRPK1 knockdown or pharmacological inhibition reduced SSRF1 phosphorylation decreasing its nuclear translocation and concomitantly RAC1b splicing. The same regulatory pathway was also found to be controlled by GSK3b. Interestingly, GSK3b phosphorylation was identified as a target for the anti-inflammatory drug ibuprofen, which inhibits RAC1b overexpression.

**Conclusions:** Together, our results demonstrate that oncogenic signal transduction pathways deregulate alternative splicing and this may be drug-reversible.

**Legal entity responsible for the study:** Peter Jordan

**Funding:** Fundação para a Ciência e Tecnologia.

**Disclosure:** All authors have declared no conflicts of interest.

**42P** Preserving tumor heterogeneity: A microfluidic reactor for ex vivo preservation of colorectal cancer biopsies


**Annex Institute of Engineering Research (I3A), University of Zaragoza, Zaragoza, Spain, Service of Digestive Diseases, University Clinic Hospital Lozano Blesa, Zaragoza, Spain, Service of Pathological Anatomy, University Clinic Hospital Lozano Blesa, Zaragoza, Spain**

**Background:** Foreseeing treatment outcome in cancer patients is still a challenge that needs to be addressed. Tumors are complex structures, where the interaction between the tumor cells and the surrounding microenvironment regulates key processes in cancer progression, such as angiogenesis, evasion and modulation of the immune system response, and invasiveness. These interactions confer tumors a high heterogeneity not only inter-patient but also intra-patient. In vitro experimental models have been developed to preserve this heterogeneity present on tumor biopsies by the use of rotary wall and perfused bioreactors. However, the complexity and size of the bioreactors prevent from visual inspection of the sample and the realization of a high-throughput screening. The present work focuses on the combination of microfabrication techniques and microfluidics to downsize classic experimental models. The developed methodology requires only microliter size sample, and allows real time optical inspection.

**Methods:** A microscopy slide size optically transparent microfluidic bioreactor (phio-reactor) was designed and developed to preserve high cellularity on complex samples through constant perfusion. Colorectal carcinoma (CRC) biopsies were taken after previous patient consent was obtained. CRC biopsies were perfused by cell culture media in the phio-reactor during one week. After perfusion, CRC biopsies were histologically processed, stained and characterized by immunofluorescence.

**Results:** High cellularity was observed in CRC biopsies after one week of perfusion. Stromal and parenchymal preservation was confirmed by both, histological staining and immunofluorescence.

**Conclusions:** The use of microfluidic bioreactors can be successfully used to preserve CRC biopsies, maintaining cell viability and tumor microenvironment under controlled conditions. The use of small sample volumes (microliters) allows high throughput screening using regular biopsy samples, a key feature to achieve personalized treatments in cancer.

**Legal entity responsible for the study:** University of Zaragoza

**Funding:** None

**Disclosure:** All authors have declared no conflicts of interest.

**44P** Role of ICAM-1/LFA-1 interaction in the angiogenic and desmoplastic response in liver metastasis


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**Background:** The colorectal cancer is one of the most common cancers in the world being the main cause of death the metastatic spread to the liver. During metastatic progression, a stromal and tumor cell crosstalk mediated by hepatic ICAM-1 and tumor LFA-1 interaction modulates the tumor microenvironment through an inflammatory and immune response. Additionally, a matrix remodeling and angiogenic response is also associated with tumor progression. The main cell type associated to these processes is the fibroblast associated to the tumor. Thus, the aim of this work is to elucidate the effect of ICAM-1/LFA-1 interaction during the angiogenic and desmoplastic response during liver metastatic progression.

**Methods:** To do so, the effect of ICAM-1/LFA-1 interaction on the tumor progression and recruitment of cancer associated fibroblasts was analyzed by an experimental metastasis assay in vivo and a modified Boyden chamber migration assays in vitro, after either activation of tumor cells with sICAM-1 or blocking of ICAM-1/LFA-1 interaction. In addition, the effects of LFA-1 tumor depletion on tumor migratory potential induced by tumor-activated fibroblasts derived factors were analyzed. Also, the effect of the modulation of this pathway on MMP’s protein and angiogenic gene expression levels was measured by zymography and qPCR, respectively.

**Results:** In vivo and in vitro assays showed an increase on fibroblast and tumor cells recruitment after activation of tumor LFA-1 activation by binding with sICAM-1 which was abrogated after blocking of LFA-1. Moreover, the expression levels of MMP9 and other prognostic factors were decreased after the blockage of ICAM-1/LFA-1 interaction. Also, the collagen deposition was increased after LFA-1 activation and diminished by LFA-1 blocking.

**Conclusions:** The interaction of ICAM-1 with tumor LFA-1 favors the recruitment of fibroblast within the tumor mediated by a modulation of pro-desmoplastic factors. This favors the remodeling of the tumor stroma and the angiogenic response and promotes tumor metastatic progression. Thus, LFA-1/ICAM-1 interaction might be pointed out as a potential target for therapy of the metastatic disease.

**Legal entity responsible for the study:** Department of Cellular Biology and Histology, University of the Basque Country, School of Medicine and Nursery

**Funding:** Basque Government

**Disclosure:** All authors have declared no conflicts of interest.
Role of discoidin domain receptors in extracellular matrix remodeling during tumor-host interaction in liver metastasis

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Background: Metastasis is the main cause of death for most solid tumors. The liver is a metastasis-susceptible organ and represents the first most common site for colorectal cancer (CRC). During tumor progression, the unique hepatic microenvironment suffers a reorganization involving the interaction between the tumor, the different hepatic stromal cells and the extracellular matrix (ECM), which is under an extreme remodeling. Among the receptors involved, discoidin domain receptors (DDR-1 and 2), a class of tyrosine kinase receptors for fibrillar collagen, are emerging as new therapeutic targets in cancer treatment, including colorectal. Aim: We aim to elucidate the implication of DDRs in the metastatic properties of the CRC cells and stromal cells in the liver.

Methods: First, the expression of DDRs on the stromal cells under tumor activated conditions and on tumor cells in the presence of tumor-activated stromal factors was assessed at protein levels. Second, this was related to the migratory potential under the same conditions. Finally, known to be induced by DDRs activation and involved in cell migration and ECM remodeling, was determined by western blot and zymography.

Results: DDRs expression was inversely altered in macropages and fibroblasts after their activation by tumor derived factors. The expression of DDRs on CRC cells was decreased by factors derived from stromal cells. These DDRs deregulated expression was related to changes in the migratory capacity of tumor and stromal cells. Moreover, MMP-9 and MMP-14 expression increased in the stromal cells activated by tumor factors, while TIMP-2 expression was higher in fibroblasts but lower in macrophages. Also, the activation of CRC cells by either fibroblasts or macropages derived factors induced a differential expression of MMP-2, MMP-9 and MMP-14.

Conclusions: The differential expression of DDRs by cells in the tumor microenvironment could redirect the expression of MMPs inducing the migratory capacity of CRC cells. In conclusion, tumor and stromal cells crosstalk may dysregulate the ECM deposition related to DDR expression contributing to the extensive stroma remodeling in CRC metastatic diseases.

Legal entity responsible for the study: University of the Basque Country (UPV/EHU)

Funding: University of the Basque Country (UPV/EHU)

Disclosure: All authors have declared no conflicts of interest.
Conclusions: Our data suggest that 5-FU induces the EMT of hepatoma cells through TGF-β, and that the higher efficacy of the combination therapy of 5-FU and IFN-β results from the inhibition of these effects of TGF-β. The differences observed between HepG2 and Huh7 cells in response to the stimulation with 5-FU indicate that the efficacy of the therapy may differ between patients with hepatitis B (HBV) or C virus (HCV) background.

Legal entity responsible for the study: Iwate Medical University

Funding: Japan Society for the Promotion of Science (JSPS)

Disclosure: All authors have declared no conflicts of interest.

49P Gene mutations involved in drug resistance in liver cancer cells using a new rna-seq data analysis workflow

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Background: According to Global Cancer Statistics (GCS) Hepatocellular carcinoma (HCC) is the 5th most common and 2nd deadliest cancer in the world. The incidence of HCC has increased over the past decades but still an effective therapy has not been developed. Sorafenib, which is the only FDA approved agent, can improve the patient survival just for a few months, therefore liver transplantation is the most efficient way of treatment up to date. In this study, we offer potential drug targets by analysing the relationship among mutation status and drug treatment response of well-differentiated Huh7 and poorly-differentiated Mahlavu liver cancer cells.

Methods: PKD/Akt pathway is hyperactive in ~94% of HCC. We determined the characteristics of the ion channels and the mRNA expression of the ion channels relative to their optimized effects. The mRNA expression data of each cancer cell line (as control) was treated with samples. Somatic mutations associated with drug resistance were comparatively identified with RNAseq data workflow wrapped in our laboratory using GATK-MuTect tool (Cibulskis, 2013). The results were further filtrated to obtain the missense mutations.

The mutated genes that were identified during the chemical knockdown studies were further analysed in patient survival data. The functional studies were performed by gene silencing.

Results: SLCT39A5, FRG1, PPHLN1 and SRP9 gene mutations were found to be shared among all drug resistant cells. Mutated genes were shown to be associated with cancer progression and aggressiveness. In addition, we found an unknown transcript called CTC512. The functional studies demonstrated that once these genes were silenced, the cellular growth was prevented. Gene silencing showed the alteration of the cell cycle progression of drug resistant cells. The affected downstream pathways were further analyzed by western blots.

Conclusions: Our results indicate potential target genes which are critical to be addressed due to their roles in resistance to drugs in HCC. Once the mutated genes are silenced, the cancer progression is prevented. The identified genes can be considered as chemotherapeutical and disease progress targets.

Legal entity responsible for the study: Rengül Cetin Atalay, METU

Funding: None

Disclosure: All authors have declared no conflicts of interest.

50P Camouflaging iRGD-EGFR anchored human cytokotoxic T-lymphocyte membrane to the surface of nanoparticles combined with low-dose irradiation: New approach to enhance drug-delivery targeting in gastric cancer

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Background: We report a biomimetic delivery platform based on human cytokotoxic T-lymphocyte membrane. In this platform, T-lymphocyte membranes were camouflaged to the surface of poly-lactic-co-glycolic acid nanoparticles, with local low-dose irradiation (LDI) as a chemo-antitransfusant. These carriers were further anchored with the recombinant protein anti-EGFR-iRGD, improving tumor accumulation, facilitating tumor uptake.

Methods: The T-lymphocyte membrane coating was verified by dynamic light scattering, transmission electron microscopy and confocal laser scanning microscopy. The particle phagocytosis study was performed using a human phagocytic cell line. In vivo NIR fluorescence imaging was performed to monitor the route of nanoparticles. EGFR expression of tumor cells was tested before and after LDI.

Results: This new platform reduced phagocytosis of macrophages by 23.99% (p < 0.002). iRGD-EGFR anchored T-lymphocyte membrane-encapsulated nanoparticles accumulated in tumor site more than unfunctionalized groups, while LDI significantly enhanced the targeting ability. LDI could up-regulate EGFR expression on tumor cells, which was important in the process of localization of iRGD-EGFR anchored T-lymphocyte membrane-encapsulated nanoparticles in tumors.

Conclusion: This new platform included both the long circulation time and tumor sites accumulation ability while LDI could significantly enhance the tumor accumulation ability.

Legal entity responsible for the study: National Natural Science Foundation of China

Funding: National Natural Science Foundation of China

Disclosure: All authors have declared no conflicts of interest.

51P Delivery of paclitaxel-loaded erythrocytes-based nanoparticles using injectable albumin hydrogel for regional chemotherapy

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Background: Peritoneal dissemination often occurs in advanced gastric cancer (GC) patient. However, systemic chemotherapy alone has limited effect on peritoneal metastases. The purpose of this work is to fabricate a regional nanomedicine delivery system with injectable hydrogel, to investigate the sustained drug release, biocompatibility, degradation, and the therapeutic efficacy on advanced GC.

Methods: The injectable hydrogel gelling at body temperature was synthesized by one-step esterification of albumin and polyethylene glycol. The paclitaxel-loaded nanoparticles (PRNP) were prepared by encapsulating the drug in erythrocytes membrane ghost and embedded into the hydrogel (PRNP-Gel). The physical and chemical performances were characterized by dynamic light scattering, electronic microscope and SDS PAGE. The drug loading content, homogeneity, degradation, drug release, drug anti tumor efficacy was also investigated.

Results: The PRNP-Gel suspension gelled in 15 min after subcutaneous injection. The diameter of PRNP in hydrogel was 133.1±1.6 nm, drug loading efficacy and content were 85.45±1.32% and 22.10±0.25%, respectively. 37.9% of the loaded paclitaxel was released in 18 h in vitro, demonstrating the sustained release properties of PRNP-Gel. No hemolysis was detected within the concentration up to 10 mg/mL, and the PRNP-Gel degraded completely in 200 h after injection. The IC50 of PRNP against MKN45 gastric cancer cells, determined by MTT, was 15.16 ng/mL. In vivo antitumor evaluation found that, the tumor growth inhibition of MKN45 on tumor bearing mice was 64.3% of PRNP-Gel group, which was higher than the PRNP (40.0%, P < 0.05) and Taxol (33.8%, P < 0.05). The average tumor weight was 74.8±40.1 mg, while they were 194.6±90.9 mg and 199.6±73.9 mg in PRNP and Taxol respectively (P < 0.05).

Conclusions: The biocompatible and degradable drug delivery system could release chemotherapeutics in a long-term and sustained manner, exhibited an enhanced drug accumulation at tumor site, resulting in the superior antitumor effect in vivo and in vitro. This work provided a new strategy of therapy for advanced GC.

Legal entity responsible for the study: Hanqing Qian

Funding: National Nature Science Foundation China

Disclosure: All authors have declared no conflicts of interest.

52P Effect of apatinib combined with 5-flourouracil (5-FU) on proliferation, apoptosis and invasiveness of gastric cancer cells

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Background: To investigate the effect of apatinib, a small-molecule tyrosine kinase inhibitor, combined with 5-FU on proliferation, apoptosis and invasiveness of human gastric cancer cells AGS, and provide experimental basis for the treatment of two drugs combination in gastric cancer in clinic.

Methods: The expression of vascular endothelial growth factor receptor 2 (VEGFR2) protein in human umbilical vein endothelial cells (HUVEC) and human gastric cancer cells were assessed by western blotting. 4-methyl-terrazolium (MTT) assay and flow cytometry were used to assess the cytotoxicity and apoptosis effects of the cells in response to control, single apatinib, single 5-FU, and apatinib combined 5-FU groups. Western blotting was used to evaluate the expression of p-Akt, proliferating cell nuclear antigen (PCNA), Caspase-3 and the invasiveness differences of the four groups were detected by wound healing assay and matrix metalloprotein-2 (MMP-2), E-cadherin gene expression were measured by RT-PCR. 5-FU Delivery of paclitaxel-loaded erythrocytes-based nanoparticles using injectable albumin hydrogel for regional chemotherapy

Conclusions: Our study points that apatinib combined 5-FU could inhibit the proliferation of AGS gastric cancer cells by down-regulating the expression of p-Akt. The invasiveness of AGS cancer cell was inhibited by reduced expression of MMP-2 and E-cadherin genes, and provides a theory basis for 5-FU and apatinib combination in clinic with advanced gastric cancer patients who failed to second-line treatment but still had a good performance status.
One tumour, two clones: An in vitro model of intra-tumour heterogeneity

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Background: Eradication of advanced disease remains elusive in the majority of cancers including soft tissue sarcomas (STS) despite advances in our understanding of the molecular mechanisms involved. Targeted therapies for STS development to date has largely relied upon data derived from all cells within a tumour sample and/or tumour cell lines. These approaches however, do not account for inherent heterogeneity of cancer cells within a single tumour and is considered an important factor that leads to treatment failure. Understanding intra-tumour heterogeneity is therefore a priority for cancer research and appropriate tumour models with sufficient availability would greatly facilitate the identification of novel targets and factors that lead to treatment resistance. We therefore aimed to develop in vitro models of STS that reflect intra-tumour heterogeneity.

Methods: We obtained tissue from patients having surgery for STS in Sheffield Teaching Hospitals and established primary tissue cultures. Short Tandem Repeat (STR) confirmed the same origin of both clones in both cases. DNA copy number profiling and gene expression microarray analysis were used for molecular characterisation of self-immortalised primary cell lines.

Results: One leiomyosarcoma (Shef-LMS 01) and one myofibrosarcoma cell line (Shef-MFS 01) established two morphologically-distinct tumour cell types (culture variants) in separate long term cultures. Karyotyping and growth characteristics confirmed that both variants in each case are tumour cells and they have remained stable in culture for over 100 passages. STR profiling confirms that in each case, both clones are derived from the same tumour. DNA copy number analysis with microarray-based comparative genomic hybridisation and gene expression analysis shows many identical somatic copy number abnormalities (SCNA) between variants, but also numerous genomic and transcriptomic differences.

Conclusions: We believe that these genomic and transcriptomic differences provide clues to downstream differences, which may be linked to increased stromal resistance to targeted treatment. These cell lines are therefore useful for the identification of novel targets and development of effective therapies for these tumours.

Legal entity responsible for the study: Abdulazeez Salawu

Funding: Weston Park Cancer Charity and Sarcoma UK

Disclosure: All authors have declared no conflicts of interest.

Docosahexaenoic acid mediates susceptible cell death through differential regulation of p62/p-eIF2alpha/NRF2 in LMP1-expressing nasopharyngeal carcinoma cells

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Background: Docosahexaenoic acid (DHA) induces apoptotic cell death through several mechanisms in cancer cells. We have previously demonstrated that DHA triggers apoptosis by increasing reactive oxygen species (ROS) accumulation and the ROS-mediated apoptosis caused by DHA is associated with Nrf2 signaling activation. Here we report that DHA-induced cell death is more susceptible through p62/p-eIF2alpha/NRF2 regulation in LMP1-expressing nasopharyngeal carcinoma (NPC) cells.

Methods: Viability of CNE-LMP1 and HONE-EVB cells was compared with CNE and HONE after DHA treatment by MTT assay. DHA-induced apoptosis was analyzed using the TUNEL assay and Western blot of cleaved form of PARP. Tissue expression of LMP-1 and p62 were observed by immunohistochemistry.

Results: Treatment of four human NPC cell lines (CNE, CNE-LMP1, HONE, HONE-EVB) with DHA for 24 hr resulted in a dose-dependent inhibition of cell growth. The DHA effect was due to the induction of apoptosis, given that DHA increased the cleaved form of PARP and the number of TUNEL-positive cells. The inhibition of CNE-LMP1 and HONE-EVB cells after DHA treatment was more susceptible. compared with CNE and HONE cells without LMP1 by MTT assay. The level of p62 and NRF2 of LMP1-NPC cells were increased after DHA pretreatment compared to control NPC cells. On the other hand, the level of p-eIF2alpha produced reverse result. The activation of Nrf2 signal seems to result from decreased Nrf2 inhibitor, Kelch-like ECH-associated protein 1 (Keap1), because DHA remarkably attenuated Keap1 expression levels. Moreover, silencing Nrf2 by small interfering RNAs inhibited the cytotoxic effect of DHA, indicating that Nrf2 activation plays a positive role in the process of DHA-induced apoptosis. Increased staining for LMP1 and p62 was observed in NPC tissues when compared with the nonneoplastic (chronic inflammation) tissues.

Conclusions: These results suggest that differential regulation of p62/p-eIF2alpha/NRF2 contributes to susceptible cell death by DHA in LMP-1-expressing NPC cells. Thus, utilisation of DHA may represent a promising therapeutic approach for chemoprevention and treatment of human NPC.

Legal entity responsible for the study: Chungnam National University

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Disclosure: All authors have declared no conflicts of interest.

Docosahexaenoic acid mediates susceptible cell death through differential regulation of p62/p-eIF2alpha/NRF2 in LMP1-expressing nasopharyngeal carcinoma cells

Inhibition of the ubiquitin-conjugating enzyme E2B restores the BCNU sensitivity of cancer cells by regulating MGMT ubiquitination

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Background: O6-Methylguanine-DNA methyltransferase (MGMT) is a DNA repair enzyme that removes the mutagenic O6-alkyl groups from guanines. 1,3-Bis (2-chloroethyl)-1-nitrosurea (BCNU), a DNA damage reagent, is known to induce cell death of tumours and the ubiquitin dependent proteolysis of MGMT. The present study aims to enhance BCNU cytotoxicity toward cancer cells by modulating MGMT dynamics.

Methods: Human nasopharyngeal carcinoma cells, including HONE-1 and TW01, and human colon carcinoma HT-29 cells were used for the BCNU treatments, siRNA knockdown, immunoprecipitation and western blot experiments. The BCNU cytotoxicity was determined using methylene blue assay. Proteins involved in MGMT ubiquitination were confirmed with immunofluorescence staining and in vitro protein ubiquitination assays.

Results: We previously identified ubiquitin-conjugating enzyme E2B (UBE2B), a DNA repair enzyme with ubiquitin-conjugating abilities, as a critical regulator of the cell cycle in oral cancer cells. A novel role of UBE2B was further revealed in regulating MGMT dynamics in nasopharyngeal carcinoma cells and colon carcinoma cells. Increased colocalization of UBE2B with MGMT was found in BCNU treated cancer cells. Depletion of MGMT or UBE2B in cancer cells resulted in decreased IC50 for BCNU. Lower MGMT expression levels were observed in UBE2B deficient cells. Overexpression of MGMT rescued the UBE2B-depleted cells from the cytotoxic consequences of BCNU, suggesting that MGMT is a downstream target of UBE2B. The E3 ubiquitin ligase RAD18, that is known as a partner of UBE2B in facilitating PCNA ubiquitination, was analyzed to investigate the mechanism of the UBE2B regulation on MGMT. Interaction of RAD18 and MGMT was observed in cancer cells, and was enhanced under the BCNU treatments. Our results also showed that UBE2B and RAD18 contribute to MGMT ubiquitination under in vitro conditions.

Conclusions: Our study indicated that the UBE2B-RAD18 regulation on MGMT plays an important role in BCNU-induced cancer cell death. Thus, UBE2B inhibition may be considered as a potential strategy for cancer treatment. (This work was supported by Taiwan Ministry of Science and Technology under the grants no. NSC 103-2320-B-006-036-MY3).

Legal entity responsible for the study: National Health Research Institutes, Tainan, Taiwan

Funding: Taiwan Ministry of Science and Technology

Disclosure: All authors have declared no conflicts of interest.

Oral squamous cell carcinoma cells were sensitized to cetuximab by Eribulin via induction of the mesenchymal-to-epithelial transition

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Background: Inhibition of EGFR signalling has emerged as a new treatment strategy for oral squamous cell carcinoma (OSCC). Previously, we found that loss of EGFR expression in OSCC was associated with EMT, and might have functional implications with regard to resistance to cetuximab, a monoclonal anti-EGFR antibody. Eribulin (a microtubule inhibitor) reportedly renders breast cancer less aggressive, and less likely to metastasise, by triggering the mesenchymal-to-epithelial (MET) transition. Here, we
trif/MyD88-dependent pathways, and promote the maturation of dendritic cells. Our results show that proT

Conclusions: The presence of cancer antigens, retarded tumor growth and prolonged the survival of immune cells via generating the appropriate cytokine milieu for their activation. The C-

Background: The TRL agonist prothymosin α (proTα) pleiotropically stimulates immune cells via generating the appropriate cytokine milieu for their activation. The C-terminal decapeptide proTα (100-109) is considered the immunologically active moiety of proTα, as it restores in vitro the deficient immune responses of cancer patients equally well to proTα, proTα (100-109) ligate TLR-4, signal through the TRIF/MycD88-dependent pathways, and promote the maturation of dendritic cells. The latter further stimulate TLR-type immune responses and prime tumor antigen-reactive T cell functions. We evaluated whether proTα and proTα (100-109) function correspondingly in vivo.

Methods: C57BL/6 mice were subcutaneously inoculated with the syngeneic melanoma B16.F1 cells. Upon palpable tumor formation, mice were intraperitoneally treated with 2 cycles of GM-CSF proTα (100-109) or proTα, in conjunction with a B16.F1-specific peptide vaccine. Tumor growth and animal survival were monitored. Splenocytes from selected animals were tested for ex vivo cytokitotoxicity by 

Table:59P

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Disclosure: All authors have declared no conflicts of interest.

Legal entity responsible for the study: University of Sao Paulo Research Foundation (FAPESP)

Acknowledgments: This work was supported by FAPESP (2010/17867-7).

Conflict of interest: There is no conflict of interest.

Conclusion: No oscillatory profile of clock genes was detected in skin of control animals, and tumor inoculation did not affect this oscillatory profile. Temporal oscillation of Bmal1 and Nr1d1 expression was reduced in adjacent skin and tumor as compared to skin of control animals. In liver and lung tissue, Per1 and Per2 oscillated in control animals, and tumor inoculation did not affect this oscillatory profile. Biofiltering oscillation of Bmal1 and Nr1d1 is in the liver was lost in tumor-bearing mice. In BAT, Per1 and Bmal1 oscillatory expression was also lost in tumor-bearing mice. In all organs analyzed, Bmal1 transcript was reduced in tumor-bearing mice when compared to control animals.

Legal entity responsible for the study: University of Sao Paulo Research Foundation (FAPESP) and National Council of Technological and Scientific Development (CNPq).

Disclosure: All authors have declared no conflicts of interest.

Is there receptor tyrosine kinases expression in lymphocytes in patients with renal cell carcinoma? First-in-human study

D. Khochenkova, V. Volkova, A. Olshanskaya, S. Aschuba, Y. Khochenkova, A. Anastasia Bondarenko, I. Tanafyev

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Background: To date little is known about receptor tyrosine kinases (RTK) expression on peripheral blood mononuclear cells (PBMC) and tumor infiltrating lymphocytes (TIL) in cancer patients. The aim of this study was to evaluate expression levels of major RTK: VEGFR1, VEGFR2, PDGFRα, PDGFRβ, FGFR2 in CD45+ population of PBMC and TIL isolated from patients with clear cell renal cell carcinoma (CCRC).

Methods: Tumor and blood samples were obtained from 20 patients with RCC immediately after surgical resection of primary tumor. Tumors were harvested into sterile antibiotic-containing RPMI 1640 medium (Gibco). TIL isolation was performed under modified protocol (Balda et al., 2015). Isolated TIL and PBMC were prepared for flow cytometry. Cells were double stained with anti-CD45 FITC-conjugated mouse antibody, and with PE-conjugated mouse antibodies to VEGFR1, VEGFR2, PDGFRα, PDGFRβ, FGFR2 (all from Biolegend) and were analyzed on NovoCyte 2000R flow cytometer (ACEA Biosciences). Expression of RTK was evaluated with Novocycle Software.

Results: Among PBMC 72.1±21.3% cells were CD45-positive. Isolated TIL contain 19.2±5.6% CD45-positive cells. PBMC and TIL express RTK. Expression levels of RTK are summarized in the table.

Table:59P

<table>
<thead>
<tr>
<th>Expression of RTK</th>
<th>PBMC</th>
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</tr>
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<tbody>
<tr>
<td>VEGFR1</td>
<td>25.6±11.4%</td>
<td>31±2.72%</td>
<td>0.699</td>
</tr>
<tr>
<td>VEGFR2</td>
<td>23.8±11.1%</td>
<td>53±2.93%</td>
<td>0.096</td>
</tr>
<tr>
<td>PDGFRα</td>
<td>48±18.9%</td>
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</tr>
<tr>
<td>PDGFRβ</td>
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<td>FGFR2</td>
<td>41±27.8%</td>
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Disclosure: All authors have declared no conflicts of interest.

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Disclosure: All authors have declared no conflicts of interest.
Conclusions: To our knowledge, this is first study that showed significant RTK expression on peripheral and RCC-infiltrating lymphocytes in RCC patients. PBMC and TIL have similar RTK expression levels.

Legal entity responsible for the study: Ethical committee, KCRB

Funding: Kidney Cancer Research Bureau

Disclosure: All authors have declared no conflicts of interest.

W. Badreldin, T. Powles, L. Menard, C. Ho-Yen, S. Kermond

Tumour Biology, Barts Cancer Institute-Queen Mary University of London, London, UK

Background: Bladder cancer affects 430,000 patients and leads to 165,000 deaths annually worldwide. With no major advances in the management of this disease in the last 2 decades, there is an urgent need to identify therapeutic targets with validated biomarkers. Overexpression of Met, a Receptor Tyrosine Kinase, was shown to correlate with poor prognosis in bladder cancer making it an attractive target. Caborzatinib, a Met inhibitor, showed clinical activity in patients with refractory bladder cancer in a clinical trial. However, little is known about how Met exactly signals in bladder cancer and there are no validated biomarkers. This study aims at unravelling Met signalling in bladder cancer.

Methods: Western blots and confocal/low light microscopy were used to assess Met signalling and its role in wound healing in Transitional Cell Carcinoma (TCC) cells. Met expression was assessed by immunohistochemistry in tissue samples (n = 64).

Results: Met is overexpressed in TCC cells and in 78% of invasive bladder cancer tissues. This was associated with a shorter median survival as compared to low Met levels (12.97 Vs 18.05 months). Stimulation of TCC cells with MET ligand, Hepatocyte Growth Factor (HGF), triggered Met activation and downstream signalling as well as wound healing, all of which were reduced with Met pharmacological inhibitors including Caborzatinib. The PI3K downstream effector AKT was highly activated upon Met activation. Moreover, C1PDK1 inhibition with D6C94 significantly inhibited HGF-dependent wound healing. Interestingly, HGF triggered rapid Met endocytosis in TCC cells. Furthermore, pharmacological inhibition of endocytosis reduced Met downstream signalling.

Conclusions: We report that Met is a major target in invasive bladder cancer. Our results further suggest that PI3K may be considered as a co-target of Met to improve patients’ outcome. It may also be developed as a biomarker to help select patients who may respond to Met targeted therapy. Finally, we report for the first time that, upon TCC cells. Met expression was assessed by immunohistochemistry in tissue samples (n = 64).

Conclusions: We report that Met is a major target in invasive bladder cancer. Our results further suggest that PI3K may be considered as a co-target of Met to improve patients’ outcome. It may also be developed as a biomarker to help select patients who may respond to Met targeted therapy. Finally, we report for the first time that, upon HGF-stimulation, Met gets rapidly endocytosed in TCC cells. Furthermore, inhibiting endocytosis reduced Met dependent signalling. All together, our results open the way for novel strategies to target invasive bladder cancer.

Legal entity responsible for the study: Queen Mary University of London

Funding: Barts Cancer Institute, Queen Mary University of London


L. Menard: Employee: AstraZeneca.

All other authors have declared no conflicts of interest.
Clinical dysregulation of DNA repair by the polynucleotide kinase/phosphatase-XRC4-DNA ligase IV in neurodevelopmental disease

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1Biochemistry, University of Alberta, Edmonton, AB, Canada, 2Biochemistry & Molecular Biology, Arnie Charbonneau Cancer Institute, University of Calgary, Calgary, AB, Canada, 3Biochemistry & Molecular Biology, University of Calgary, Calgary, AB, Canada, 4Oncology, Cross Cancer Institute, Edmonton, AB, Canada, 5Molecular Biophysics & Integrated Biomsgnry, Lawrence Berkeley National Laboratory, Berkeley, CA, USA, 6Molecular and Cellular Oncology, University of Texas M. D. Anderson Cancer Center, Houston, TX, USA

Background: If not repaired, DNA double-strand breaks (DSBs) can lead to genomic instability and cell death or neoplastic transformation. The major DSB repair (DSBR) mechanism in higher eukaryotes is non-homologous end-joining (NHEJ). In NHEJ, polynucleotide kinase/phosphatase (PNKP) is the primary enzyme for processing ab-normal 5'-OH and 3'-phosphate ends that prevent the final repair step by XRC4/ DNA Ligase IV (Lig IV). This processing step is thought to be mediated by an interaction between the PNKP-FHA domain and CK2-phosphorylated XRC4 C-terminal tails.

Methods: Our binding assays show tight binding between XRC4/Lig IV and PNKP both with and without CK2-phosphorylation of XRC4. Low-resolution ensemble structures of purified phosphorylated-XRC4/Lig IV/PNKP ternary complex by small-angle X-ray scattering (SAXS) experiments also suggest a second phosphorylation-independent interaction between the PNKP and XRC4/Lig IV. Hydrogen-deuterium exchange (HDX) experiments have identified a candidate for this secondary interaction site within a loop in the PNKP phosphatase domain. This site contains the clinically significant PNKP E326K mutation found in the severe form of the hereditary neurological disease MCSZ (microcephaly with early-onset intractable seizures and developmental delay). Activity assays show that the E326K mutation decreases both substrate binding and turnover in PNKP when bound to phosphorylated-XRC4/Lig IV. Furthermore, UV laser microirradiation in cells show that the E326K mutation also disrupts recruitment of PNKP to DNA lesions.

Conclusions: We have identified a putative secondary interaction site that functionally contributes to recruitment and catalysis of PNKP in NHEJ. Disruption of PNKP in this region may result in decreased DNA double-strand break repair in cells and describe a molecular basis of MCSZ. Further, PNKP has other known clinical neurological significance and its presence on chromosome arm 19q has interesting implications in oligodendrogliomas. This interaction surface may prove an interesting target for small-molecule inhibition of DNA strand break repair toward novel radio- and chemosensitizing therapies in cancer treatment.

Legal entity responsible for the study: University of Alberta

Funding: Canadian Institutes of Health Research, Alberta Cancer Foundation, Structural Biology of DNA Repair Machines Consortium.

Disclosure: All authors have declared no conflicts of interest.

Effects of rottlerin and genistein through EF2K on proliferation, invasion and cell cycle/death in neuroblastoma cells

M.A. Erdogan, O. Alkan Yılmaz

Physiology, Ege University Faculty of Medicine Department of Physiology, Izmir, Turkey

Background: Neuroblastoma (NB) is the most common extracranial solid cancer in childhood and the most common cancer in infancy in the world. Rottlerin, a naturally occurring polyphenol compound derived from Mallotus philippinensis, appears to have great potential in cancer therapy because of its effects on proliferation and apoptosis. Genistein is a phytoestrogen and it has been found to inhibit uncontrolled cell growth and level of neoplastic cell growth in several cancers. Recently, we learned that eukaryotic elongation factor-2 kinase (EF2K) is dramatically upregulated in many cancer cells and promotes cell survival and proliferation. Rottlerin and genistein have also shown inhibitory effects on this kinase in other solid tumours like pancreatic cancer. With this in mind, we investigated the effects of rottlerin and genistein in neuroblastoma cells.

Methods: In this study, two human neuroblastoma cancer cell lines (SH-SY5Y and Kelly) were treated with rottlerin and genistein in vitro. Cell proliferation, colony formation and invasion were assessed, and wound-healing tests, western blots (wb), cell cycle and apoptosis analysis by flow cytometry were performed.

Results: Our results showed that rottlerin and genistein treatments caused a significant reduction in cell proliferation, colony formation, and invasion/wound-healing capacity in neuroblastoma cells at concentrations of 5 μM and 30 μM, respectively (p < 0.0001). The combination of these doses also increased the level of inhibition in these analyses (p < 0.0001). Additionally, these drugs also increased the level of apoptosis and caused G1 cell cycle arrest in neuroblastoma cell lines (p < 0.0001). We showed that these treatments markedly inhibit EF2K overexpression. Our wb data suggested that EF2K may enhance tumorigenesis/metastasis through the upregulation of pro-tumorigenic/metastatic pathways in these cells and these agents may produce their anti-proliferative, anti-metastatic and apoptotic effects through EF2K downregulation.

Conclusion: In conclusion, these results indicate that rottlerin and genistein have important effects on neuroblastoma cell behaviour and these effects may be caused by downregulation of EF2K.

Legal entity responsible for the study: Mumin Alper Erdogan

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Influence of emetogenic brain structures on tumor growth in the experiment

E. Korobeynikova1, E. Rastorguev2, N.S. Kuznetsova2

1Laboratory Center, Rostov Research Institute of Oncology, Rostov-on-Don, Russian Federation; 2Neuromolecular Laboratory, Rostov Research Institute of Oncology, Rostov-on-Don, Russian Federation

Background: Stress is the pathogenic basis of many diseases. It leads to decreasing resistance of the organism, including antitumor one. Emotional stress of a cancer patient affects the quality of life and treatment outcomes by decreasing the antitumor resistance. Therefore, correction of emotional state is an urgent task. The purpose of the study was to reveal the influence of stimulation of emetogenic brain structures on the antitumor resistance of animals with cancer.

Methods: Transplantable solid sarcoma S45 in white outbred male rats weighing 230-250 g was used as a model of tumor growth. Implantation of bipolar stimulating electrodes in the subcortical structures of the brain was performed stereotactically.

Table: 65P

<table>
<thead>
<tr>
<th>Structure</th>
<th>LS</th>
<th>GP</th>
<th>Controls</th>
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</thead>
<tbody>
<tr>
<td>n</td>
<td>9</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Initial tumor V (cm³)</td>
<td>3.0 ± 0.5</td>
<td>3.1 ± 1.9</td>
<td>2.2 ± 1.2</td>
</tr>
<tr>
<td>Final tumor V (cm³)</td>
<td>4.7 ± 1.1</td>
<td>7.5 ± 2.2</td>
<td>6.8 ± 1.6</td>
</tr>
<tr>
<td>Tumor increase (%)</td>
<td>53.3 ± 2.8</td>
<td>186 ± 6.5</td>
<td>211 ± 6.8</td>
</tr>
<tr>
<td>Effectiveness index</td>
<td>0.4</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Inhibition of tumor growth (%)</td>
<td>3.8</td>
<td>10.2</td>
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Morphological study of the thymus, spleen and lymph nodes of animals with LS showed signs of high functional activity of the organs providing a high level of resistance.

Conclusions: Electrostimulation of LS influences antitumor resistance, significantly improving it. This suggests the expediency of combining specific anticancer drugs and non-specific effects of psychotropic drugs - anxiolytics in complex treatment of cancer.

Legal entity responsible for the study: Rostov Research Institute of Oncology

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Systematic evaluation of the immune microenvironment of neuroendocrine tumours (NET)

G. Veselić, A. Childs, Y.N.S. Wong, O. Ogubršć, T.V. Luong, C. Thirlwell, M. Caplin, T. Marafioti, S. Quezada, T. Meyer

1UC Cancer Institute, UCL - University College London, London, UK, 2Department of Surgery, Royal Free Hospital, London, UK, 3School of Medicine, Royal Free Hospital School of Medicine, London, UK

Background: Immunotherapy is currently being explored in many tumour types with encouraging results, but has not yet been evaluated in neuroendocrine tumours (NET).

Our aim is to characterise the immune landscape of NET and determine which immune-modulatory pathways control the tumour infiltrating lymphocytes (TILs) in order to develop a rational approach for immunotherapy in this tumour type.

Methods: Peripheral blood and fresh tissue was obtained from consenting patients with NET, and subjected to multicolour flow-cytometry to determine the abundance of CD4+, CD4+FoxP3- effectors (CD4ef), and CD4+FoxP3+ regulatory (Treg) T cell subsets and the expression of co-inhibitory and co-stimulatory checkpoint molecules on these subsets. Additionally, matched FFPE tissue was obtained for multiparametric immunohistochemistry to investigate the distribution of the immune infiltrate.
Results: Tissue from 23 NET patients including 19 mid-gut tumours (13:G1 and 6:G2) was analysed. Overall the tumours contained a higher proportion of Tregs compared with peripheral blood (8.5% vs 5%, P = 0.02) and had a CD8/Treg ratio of 18:1:2.3 respectively (P = 0.036). The co-inhibitory molecules CTLA-4 and TIM-3 showed highest expression on Tregs, while PD-1 and LAG-3 expression was similar across all T cell subsets. Co-stimulatory molecules, including ICOS, 41BB and OX-40, were also highest on Tregs, as was the recently identified co-stimulatory receptor TIGIT. Immunohistochemistry revealed that the majority of cases have <1% intratumoral CD4+ and CD8+ T cells but a higher number of peritumoral T cells from all subsets. Where present, T cells were predominately CD8+ and intratumoral CD163+ macrophages were also identified.

Conclusions: These preliminary results provide novel insight into the immune landscape of NET, and may inform the development of targeted combination immunotherapies. Initial results suggest that checkpoint molecules, such as PD1 and LAG-3, may be potential targets in this tumour type and work is ongoing to further elucidate the immunogenic potential of NET.

Legal entity responsible for the study: University College London

Funding: None

Disclosure: All authors have declared no conflicts of interest.

67P Developing a prediction model for response to lenalidomide treatment in refractory/refractory relapsed multiple myeloma patients

Precision Medicine Research Center, The Catholic University of Korea, College of Medicine, Seoul, Republic of Korea

Background: Despite improvements in treatment for Multiple myeloma (MM) achieved by novel drugs such as proteasome inhibitors (bortezomib) and immunomodulatory drugs (IMiDs), most patients will ultimately relapse or become refractory to their current treatment. Therefore, it is important to understand the mechanisms of therapeutic resistance in relapsed/refractory MM (RRMM) for improving treatment outcome. Recently, it was reported that serum or plasma of MM patients showed sufficiently stable miRNA signatures with prognostic impacts in MM cohorts, which can be used as minimally invasive markers for predicting and monitoring treatment outcomes. However, the expression patterns and biological implications of miRNAs are still unclear in RRMM patients receiving lenalidomide with dexamethasone (Len-dex).

Methods: We investigated the expression of serum miRNAs by genomewide miRNA array analysis and explored their predictive values in RRMM patients receiving Len-dex.

Results: We explored the associations of miRNAs with treatment outcome of Len-dex treatment and progression in 55 RRMMs (25 good responders and 30 poor responders) and built a prediction model for treatment response. Three miRNAs (miR-29c-3p, miR-30c-5p, and miR-331-3p) were found to be significantly down-regulated in poor responders. In survival analysis, lower expression of the three miRNAs was significantly associated with shorter time to progression (TTP) or poorer overall survival (OS). Eight clinical factors were also associated with TTP or OS. By combining the miRNA markers and clinical markers, we designed a prediction model for response to lenalidomide treatment in RRMM patients. Our model showed better prediction power than the clinical factors alone (AUC = 0.855, sensitivity 84%, specificity 76%, and accuracy 81%) than international staging system (ISS) based prediction.

Conclusions: Our results suggest the potential of circulating miRNAs as minimally invasive markers for treatment response and progression in RRMM patients.

Legal entity responsible for the study: The Catholic University of Korea

Funding: None

Disclosure: All authors have declared no conflicts of interest.

68P Combinatorial inhibition of mTOR and exportin-1 (XPO1) represses cell survival via metabolic modulation of pro-survival pathways in mantle cell lymphomas

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Background: MCL is an aggressive B-cell lymphoma with aberrant expression of several oncogenic effectors and requiring novel anticancer strategies. The nuclear trans- porter exportin-1 (XPO1) is highly expressed in MCL and is critical for cancer survival and proliferation. mTOR signaling is frequently activated and an important therapeutic target in MCL. In this study, we investigated the antitumor effects and molecular/metabolic changes induced by combinational dual mTOR inhibitor AZD-2014 and XPO1 inhibitor KPT-185 on MCL cells under the hypothesis that mTOR inhibition by AZD-2014 represses KPT-185 induced deregulation of glycolysis.

Methods: Four MCL cell lines (Jeko-1, X138, JVM-2, and MINO), primary MCL cells, and normal bone marrow samples were utilized. Cell viability was evaluated by MTT assay. Cell cycle and apoptosis were determined by flow cytometric analysis. cDNA array, ITRAQ proteomic, immunoblotting and metabolome analysis using CE-TOF-MS were also performed.

Results: AZD-2014 enhanced KPT-185-induced the inhibition of cell growth and repression of cell viability in MCL cells but not in normal bone marrow cells. Different mTOR inhibitors (AZD-8055 and MLN0128) demonstrated similar effects. AZD-2014 + KPT-185 decreased expression of the oncogenic mediator c-Myc and the translational transcriptional network regulator HSF1 as detected by immunoblotting. ITRAQ proteomic analysis demonstrated that the combination caused repression of ribosomal biogenesis. Treatment with either AZD-2014 or KPT-185 depressed phospho-S6. GSE-OF-MS metabolite assay showed that AZD-2014 + KPT-185 inhibited the ecbeks cycle and that AZD-2014 effectively repressed KPT-185-induced upregulation of glycolysis. cDNA array detected downregulation of NOD2 which is known to trigger activation of MAP kinases and of NF-kappaB signaling. Moreover, AZD-2014 + KPT-185 activated AMPK, an energy stress marker in a cell type-dependent manner.

Conclusions: Our findings indicated that the combinatorial inhibition of mTOR and XPO1 identifies a novel synthetic lethality mechanism that could be exploited clinically, following satisfactory completion of pre-clinical in vivo studies.

Legal entity responsible for the study: Yoko Tabe

Funding: None

Disclosure: All authors have declared no conflicts of interest.

69P CD200 and indoleamine 2,3-dioxygenase-1 (IDO-1) overexpression in relapsed acute myeloid leukemia patients

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Background: Immunosuppression is one of the major causes of AML pathogenesis and progression. CD200 and IDO are immunoregulatory factors which overexpressed in some solid tumors and hematological malignancies. Distinct researches have shown CD200 and IDO expression is associated with AML progression. In the current study, we simultaneously examined the expression of these molecules, as the two important factors including in immunosuppression, in the newly diagnosed and relapse AML patients to investigate their correlation with each other.

Methods: 48 PBMC samples of newly diagnosed and relapse AML patients were tested and also 32 normal subjects were employed as control. CD200 expression level was examined on cells by flow cytometry and quantitative real time RT-PCR was used to determine the IDO-1 gene expression. Finally, data were analyzed statistically.

Results: Data showed that CD200 and IDO-1 overexpressed especially in relapsed patients. Comparison between FAB AML subgroups demonstrated no statistical difference in the case of CD200 level but expression of IDO-1 was slightly increased only in M4 subgroup in comparison to M3. Correlation analyses showed strong association between expression of CD200 and IDO-1 in all patients particularly in relapsed AML, whereas no significant correlation was found in normal subjects.

Conclusions: According to the role and overexpression of CD200 and IDO-1 in AML patients and also their two-way correlation with T-reg in disease induction and progression, simultaneous assessment of these parameters are so valuable for more exact prognostic detection. Also inhibition of all these immunoregulatory pathways could be so useful for immunotherapy outcome, especially in relapsed AML.

Legal entity responsible for the study: Tehran University of Medical Sciences

Funding: None

Disclosure: All authors have declared no conflicts of interest.

70P Correlation between types of acute lymphoblastic leukemia with socio demographic factors

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Background: Acute lymphocytic leukemia (ALL) is the most predominant hematopoietic clonal disorder in children than adult. ALL classifies into two subtypes: B—ALL and T—ALL. The incidence of ALL subtype in urban areas is generally higher than rural areas. In the Western World, the predominant immunophenotype observed in ALL is B—ALL with 60-80% of total case, and T—ALL is only 15-20%. But in case of developing country like India the reverse is true. The objective of the present study is to examine and correlate T—ALL and B—ALL in leukemia patients with respect to socio-demographic factors.

Methods: During May 2015 - April 2017, total 427 ALL patients (male:female::1.9:1), age between 2-60 years attended OPD and IPD of Netaji Subhas Chandra Bose Cancer Research Institute, Kolkata, India. We have collected peripheral blood and/or bone marrow samples for immunophenotyping by FACs after taking written consent from the patients. Each sample is evaluated with a panel of monoclonal antibodies and compared the immunophenotyping data with socio-demographic factors (age, sex, economic and social status etc).

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Disclosure: All authors have declared no conflicts of interest.
Results: The overall survival of ALL patients (with mean age 13.6 years) in 2 year is 73.6%. In our hospital, the economically weak patients (77.05%) are more abundant than economically sound patients (22.95%). Out of 427 patients, T-ALL (51.28%) is predominant among B-ALL (48.71%). We found that immunophenotyping data is correlated with all the socio demographic data i.e., sex, economic and social status etc. Though disease free survival and event free survival is marginally higher in B-ALL compared to T-ALL, but we found the survival of T-ALL is also increasing.

Conclusions: Our unique findings emphasize that the detection of DS-L and B-ALL by immunophenotypic analysis for better treatment and outcome of the patients and also trying to correlate the prevalence of T-ALL and B-ALL with economical status and also with other socio-demographic factors in study area.

Legal entity responsible for the study: Netaji Subhas Chandra Bose Cancer Research Institute

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CALR mutations and their link with cellular calcium during megakaryocyte hyperplasia in MPNs

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Background: Megakaryocyte hyperplasia is a major characteristic of two myeloproliferative neoplasms (MPNs) known as essential thrombocythemia (ET) and Primary myelofibrosis (PMF). About 35% of ET and PMF patients harbour somatic calreticulin (CALR) mutations. In ET and PMF, elevated Ca2+ buffering protein within the endoplasmic reticulum (ER), Ca2+ is an important element for megakaryocyte functions; however the effect of CALR mutations in cellular Ca2+ during megakaryocyte hyperplasia remains elusive.

Methods: In-TASSER software was used to study the aminoacid charge using the 3D structure of CALR mutant. Marimo cells and overexpressing CALR mutant HEK293T and DAMI cells were used as cellular models. CALR cellular localization was addressed by flow cytometry and confocal microscopy. Basal Ca2+ levels were measured by Fluo-8 staining. Furthermore cells were treated with Fendiline and BTP-2 calcium channel blockers to manipulate cellular Ca2+.

Results: The present study shows that CALR mutations change the aminoacid charge of the Ca2+ binding region of CALR mutant. Calcium is localized outside the ER, within the cytoplasm and the cellular membrane. These results suggest that CALR mutations could be affecting the Ca2+ buffering activity within the ER. Therefore, we further analysed Ca2+ basal levels in CALR mutant cells, and our results showed that CALR mutations show lower cellular Ca2+ levels. These results lead us to think that low intracellular Ca2+ levels could be the driving force of megakaryocyte hyperplasia characteristic of ET and PMF. Therefore, we induced low intracellular Ca2+ levels in leukemic blasts by using Ca2+ channel blockers and our results showed that treated cells display an increase of the megakaryocyte marker CD41a in the cell surface, suggesting an induction of megakaryopoiesis in these cells.

Conclusions: These findings elucidate how low intracellular Ca2+ caused by CALR mutations could be the driving force of megakaryocyte formation in ET and PMF. This study shows the relevance to understand the role of cellular calcium during megakaryocyte formation and this could unravel the pathway of CALR mutant in MPNs.

Legal entity responsible for the study: University of Salford

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Approach based on magnetic nanocomplexes improves antitumor efficacy of dendritic cells immunotherapy in mice

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Background: Dendritic cell (DC)-based immunotherapy represents a promising approach for cancer treatment. However, the DC homing to the lymphoid tissues is poor, thus hindering the activation of antigen-specific T cells and reducing their antitumor efficacy. Here, we developed an approach based on magnetic nanoparticles (NP) to manipulate DC migration and thus elicit a more robust and efficacious antitumor response in tumor-bearing mice.

Methods: Mouse spleen DCs were loaded with nanocomplexes (NC) consisting of iron oxide NP (8x1012 g/cell) and lyophilized tumor tissue. To investigate the presence of NP in DCs, the method of Fe2+ and Fe3+ detection by Prussian Blue Staining was used. DCs were injected intradermally into tumor-bearing mice in an amount of 2x107 per mouse at an interval of 3 days starting from day 0 after Lewis lung carcinoma inoculation. One group of mice that received DCs loaded with NC was exposed to a magnetic field for 1 h. The number and volume of metastases and tumor weight were assessed 28 days after tumor inoculation. At the same time, the levels of INF-γ, IL-10, TGF-β, IL-4, Foxp3 mRNA expression in the spleen and inguinal lymph nodes were determined.

Results: The iron oxide NP showed no toxic effects on the DCs and had no effect on their viability. We found that almost all DCs are able to incorporate magnetic NP after 24h of incubation. Fewest metastases were found in the mice that received DCs loaded with NC and were exposed to a magnetic field: the number of metastases in mice from this group was 1.7 times less than in control mice. It should be noted that the volume of metastatic nodes in the lungs and the mass of the primary tumor were practically the same as in the control mice. The most pronounced decrease in Foxp3 mRNA levels in the lymph nodes, indicating a decrease in the activity of regulatory T cells, was also noted in the mice receiving DCs loaded with nanocomplexes and exposed to a magnetic field. In the mice of this group, a significant decrease in the level of IL-4 in the spleen was detected.

Conclusions: Our results suggest that an approach based on magnetic NC could be a promising strategy for improving the antitumor efficacy of DC-based immunotherapy.

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Signs of tumor-specific immune processes in the regression of large rat tumors under the influence of low-intensity EMR EHF and magnetic nanoparticles

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Background: The problem of elaboration of methods for effective mobilization of immune antitumor processes remains urgent. Earlier, it was shown that regression of experimental animal tumors can be achieved under the influence of low-intensity electromagnetic radiations (EMR) and magnetic nanoparticles (NPs) (Garkavi L.H. et al, 1996; 2013). The aim of the study was to determine the possibility of regression of large transplanted tumors of white rats under the influence of low-intensity EMR of millimeter range (EHF) and magnetic NPs.

Methods: In experiments on 123 white outbred male rats (200-300g) with transplanted Pluas lymphosarcoma - low-intensity EMR EHF (42.2 GHz, 10 mW/cm2), exposure 15-30 min, low-frequency modulation) and magnetic NPs (10 ± 2 nm) in the form of the magnetic fluid AM-01 (“AM-Cube”, Ekaterinburg) were used. The EMR acted on the animal’s head starting 3 days before the tumor was transplanted. NPs were injected into peritoneal zone 2-3 times a week in a single dose of 17.7 mg/kg to animals with already formed tumors. Duration of treatment was 4 weeks. We studied the dynamics of tumor size, histochemonical and cytometric changes in tumor tissue. The Wilcoxon test was used to evaluate the results.

Results: When EMR EHF was used, complete regression of tumors with a size of 5-6 cm3 and a partial regression (by 30-40%) of tumors with a size of 10-13 cm3 were noted. The effect was obtained in 53% of the animals. In cases of using magnetic NPs, tumor regression was observed in 40% of the animals, complete regression of tumors with a size of 5-30 cm3 was observed. Before the regression began, the tumor growth rates did not differ from those in the control group when using as one of the other factor. In addition, the regression was characterized by a rapid rate (5-7 days) and no signs of intoxication in animals. In the peritumoral area considerable macrophage activity and increasing number of cytotoxic T-lymphocytes were noticed.

Conclusions: The timing of the onset of regression, its dynamics and the absence of signs of intoxication during rapid elimination of large tumors indicated the deployment of antigen-presentation processes and specific killing of tumor cells by inducing apoptosis.

Legal entity responsible for the study: Rostov Research Institute of Oncology, Ministry of Public Healthcare of the Russian Federation

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Stimulation of RAC1/PAK1 signalling upregulates DNA damage repair genes via the BCL6/STAT5-switch

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Background: Colorectal cancer is one of the most prevalent types of cancer worldwide. The GTPase RAC1 and its effector PAK1 have been found overexpressed or hyperactivated in this type of cancers, particularly those with more aggressive and invasive features, which is frequently correlated with resistance to chemotherapy and unfavourable clinical prognosis. Previously, we described a new signalling pathway in


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which activation of RAC1/PAK1 signalling promotes a transcriptional switch between the BCL6 repressor and the STAT5 transcriptional activator at a restricted subset of gene promoters.

Methods: Here we used a novel combinatorial ChIP-Seq approach for the genome-wide identification of the BCL6/STAT5 switch target genes.

Results: Ontological enrichment analysis among the identified target genes revealed an overrepresentation of genes involved in DNA damage repair. Using the comet assay as readout for the extent of DNA damage, we show that the activation of RAC1/PAK1 signalling significantly accelerates DNA damage repair through the upregulation of p53.

Conclusions: This work highlights an additional role for the RAC1/PAK1 signalling axis that may contribute to the chemoresistant phenotype of aggressive colorectal tumours.

Legal entity responsible for the study: Paulo Matos

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Disclosure: All authors have declared no conflicts of interest.

77P Deciphering the regulation of the metastasis suppressor, NDRG1 in different cancer-types and its functional implications

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Background: The metastasis suppressor, N-myc Downstream Regulated Gene-1 (NDRG1) inhibits metastasis in a variety of cancer-types, including cancers of the breast, colon, pancreas and prostate. Its potent anti-oncogenic effects were demonstrated in multiple in vitro and in vivo studies, making it a promising therapeutic target. However, exactly how NDRG1 is regulated in different cancer-types and how different regulatory mechanisms affect NDRG1 function remain to be elucidated. Notably, post-translational modifications (PTMs), phosphorylation and cleavage of NDRG1, have been associated with its function. Therefore, it was crucial to examine whether these PTMs occur universally or selectively in different cancer-types. Further, considering the DNA repair role suggested for nuclear NDRG1, the effects of the above PTMs on nuclear NDRG1 levels was examined.

Methods: DU145 and PC3 prostate cancer cells, PANC-1 pancreatic cancer cells, HCT-29 colon cancer cells, HepG2 and Hep3B hepatocellular carcinoma (HCC) cells were utilised. Full-length (FL) and truncated (T) NDRG1 isoforms were detected using a C-terminal directed antibody. Ser330 or Thr346 phosphorylation (p-NDRG1) was detected using specific antibodies.

Results: For the first time, we demonstrated that phosphorylation and potential cleavage of the NDRG1 protein occurs in all the various cancer cell-types examined. Although the levels varied, both the FL and T NDRG1 and its phosphorylated form were detected in all tumour cells assessed. The FL NDRG1 isoform was predominantly found in the cell nucleus. Ser330 p-NDRG1 was also highly localised in the cell nucleus, while Thr346-p-NDRG1 was mostly cytoplasmic. These cellular distribution patterns were similar in all cancer-types tested.

Conclusions: This study demonstrates for the first time that the NDRG1 protein is phosphorylated and potentially cleaved in diverse cancer cell-types. Further, FL NDRG1 and Ser330 p-NDRG1 were highly localised to the cell nucleus. These results indicate that the N-terminal region and phosphorylation at Ser330 could be crucial for nuclear expression and the well-known anti-metastatic function of NDRG1.

Legal entity responsible for the study: The University of Sydney

Funding: The University of Sydney, Cancer Institute New South Wales National Health and Medical Research Council, Cancer Australia, Cure Cancer Australia Foundation.

Disclosure: All authors have declared no conflicts of interest.

78P Registration-based automated lesion detection and therapy evaluation of tumors in whole body PET-MR images

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Background: Integrated PET/MR scanners can simultaneously acquire whole body functional PET data together with morphological and functional MR data. Whole-body PET-MRI datasets contain huge amounts of spatially detailed morphological, functional and metabolic information. We propose a method, based on deformable registration to a whole-body atlas, for computer aided detection of lesions in image data from an integrated PET-MRI system.

Methods: Images were acquired using an integrated 3T PET-MRI system (Signa PET/ MR, GE Healthcare). Fat and water MR images were collected using a Dixon MR

Attenuation Correction (MRAC) sequence (TE 1.67ms, TR 4.05ms, voxel size: 2x2x2.5 mm). Subjects underwent a PET scan after injection of [F18]-FDG (2 MBq/kg) with 3 minutes per bed, with a 100-120 minute interval between injection and scan start. PET reconstruction was performed using GE’s fully 3D Time-Of-Flight iterative reconstruction (2 iterations, 28 subsets, standard 5 mm filter, voxel size: 3.125x3.125x2.78). Deformable image registration was used to spatially align subjects to a previously created morphological and functional whole-body imaging atlas (Ekstrom et al., ISMRM 17), to allow voxel-wise comparisons between the imaged subjects and the atlas. Each voxel in the atlas contains mean and standard deviation of the PET uptake. Utilizing the knowledge that low ADC-values (low diffusion measured by MRI) and high FDG uptake (high metabolism measured by PET) is indicative of malignancy, suspected lesions can be detected by measuring how much the FDG uptake in each voxel deviates from “normality”, as defined by the atlas. This approach generates a voxel-wise “lesion probability map” for the imaged subject. The same registration approach can be used to quantify longitudinal changes in detected lesions, for treatment evaluation.

Results: Lesion probability maps have been generated for patients with manually identified lesions, correctly assigning high values to the regions manually identified as suspected lesions.

Conclusions: The proposed method is promising for lesion detection in whole body PET-MRI images. Future work includes quantitative verification of the accuracy of the detected regions, comparing with a radiologist.

Legal entity responsible for the study: Uppsala University

Funding: Antaros Medical

Disclosure: H. Ahlström, J. Kullberg: Co-founder and owner of Antaros Medical. All other authors have declared no conflicts of interest.

79P 1,3,5-s-triazine containing analogues as a prime Src family inhibitor: Design synthesis docking, anticancer and angiogenic inhibition efficacy on cancer grafted CAM

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Background: The importance of angiogenesis for solid tumor growth is well recognized and evident by the vast differential of research devoted to the subject for over thirty years. It is a complex process directed by growth factors, receptors, extracellular matrix (ECM)-to-cell and cell-cell interactions. Tyrosine kinase (TKs) is the protein enzymes catalyze the transfer of a phosphate group from an ATP molecule to a tyrosine residue of the target protein, thus leading to signal transduction. Cytoskeletal TKs such as Src, Abl and Lck have been to date discovered and characterized and found that in-activation signalling pathway. A special Src protein like FAK is a non-receptor protein-tyrosine kinase which has vital role in various cellular function like cytoskeleton reorganization, migration, adhesion, spreading, configuration and destruction of FA, cell protrusions, progression, proliferation and apoptosis. The functional alteration of Src signal may be the reason for cancer and metastasis. So this can predict that Src and their signal inhibition can utilized in cancer therapy. Triazine containing hybrid analogues act as a prime skeleton to inhibit Src family TKs like FAK so in present project we constructed 1,3,5-triazine containing analogues (TCA) as an effective cancer induced angiogenesis inhibitor.

Methods: TCA analogues constructed accordingly similarity field positioning and pattern through forge V10. Further more in-silico simulation was done using autodock for most prominent analogues. The analogues derived via multifactorial synthetic protocol. The activity evaluation proceeded via in-vitro assay against MCF-7 (Breast cancer) cell line and further in-vivo antiangiogenic potency evaluated against cancer induced chorioallantoic membrane

Results: The newly designed and constructed TCA heterocycles expressed more than 56% of similar field point pattern and intra atomic alignments. The prominent pattern shown by the analogue 8d (chloro-anilino) and 8k (bromo-anilino). In-silico docking on hydrophobic site of Src family protein (PDB: 4BKS) revealed that analogue 8d have binding with CY502, TR503, GLU506, ILE428, ASN551 while analogue 8k showed interaction with THR503, GLU506, ILE428, LEU567, ASN551 amino acid residue which was similar like vendatinib. Biological evaluation showed that analogues 8d and 8k have great tendency to inhibit cancer induced angiogenesis with marginal toxicity profile.

Conclusions: We have developed a significant series of anticancer analogues and proved the site of binding on the surface of Src family TKs receptor FAK.

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A new isoquinoline alkaloid bersavine as a possible anticancer agent

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Background: Plants have had crucial role in the folklore of ancient cultures for over 5000 years. In addition to the use as food or spices, plants have also been utilized as medicine. Two remaining living traditions, the traditional Indian and Eastern medicine, have contributed most to the current state of knowledge related to medicinal plants. In their folklore, herbal medicines were prepared e.g. as teas or tinctures. These products are used as complementary treatment alongside conventional drugs till today. Another trend begun in the early 19th cent., which involved the isolation of active compounds from plants. This tendency led to the discovery of the analgesic alkaloids morphine and codeine or the cardiac glycoside digitoxin. Recently, a new alkaloid bersavine was isolated from Berberis vulgaris, along berbamine and berberine.

Methods: The dried root bark from Berberis vulgaris was minced and extracted with EtOH. The extract was evaporated, dissolved in HCl and extracted with nonpolar solvents. Subsequently was executed preparative TLC, which reveal a yet unknown alkaloid, later identified by MS and NMR analysis and named bersavine. Effect of bersavine on viability and proliferation was evaluated by WST assay and Trypan blue staining. Next was analysed its impact on cell cycle and apoptosis using the flow cytometry, activity of caspases and Western blot analysis of regulatory proteins was implemented.

Results: Bersavine’s effect on cancer cells was first evaluated on panel of 9 different cell lines. Cancer cell lines MOLT-4, Jurkat, HT-29, HeLa and MCF-7 appear to be the most sensitive to the effect of bersavine. Follow-up experiments revealed that bersavine reduced cell viability and proliferation in a dose dependent manner within 24 h of treatment. Moreover, it induced apoptosis even more pronounced 48h following the treatment. The decrease in cell viability was caused by the induction of apoptosis and activation of caspases.

Conclusions: All acquired results suggest that bersavine has very promising activity and it would be worthwhile to subject it to further evaluation.

Legal entity responsible for the study: Charles University, Faculty of Medicine in Hradec Kralove

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The impact of co-culture of NSCLC tumor cells and fibroblasts on drug response

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Background: The role of stromal cells and the tumor microenvironment has been described to modulate cancer development in vivo and drug response. This study was performed to evaluate the effect of different types of fibroblasts and their interaction with NSCLC tumor cell aggregates.

Methods: Non Small Cell Lung Cancer (NSCLC) tumor cell aggregates were microencapsulated in alginate capsules, alone or in combination with fibroblasts (immortalized normal and cancer-associated fibroblasts – NFs and CAFs, and human dermal fibroblasts – hDFs), cultured during four weeks; and tumor growth and drug response, both in vitro and in vivo, were evaluated.

Results: Microencapsulation of H1650 and H4347 spheroids in mono- or co-cultures with fibroblasts resulted in viable cultures with tumor aggregate increasing continuously during culture time. However, tumor growth in vitro co-cultures was dependent on the source of fibroblast and cell line used. When challenged with drugs, co-cultures with fibroblasts in our in vitro 3D model presented, in general, lower sensitivity to therapy after 3 weeks of treatment. H1437 + hDFs co-cultures showed less sensitivity to vasoarbit treatment, with higher DNA concentration (2-fold higher versus mono-cultures) and higher resazurin reduction activity (35% versus 22% in mono-cultures). H1650 + NFs co-cultures also demonstrated lower sensitivity to erlotinib and docetaxel treatment, with higher resazurin reduction activity (71% versus 29% in mono-cultures) and higher viable area of aggregates, respectively. Mono and co-cultures can also be injected in mice for the generation of xenografts. Evaluation of tumor growth based on the local of injection, fibroblast source and drug response was performed. In agreement with the in vitro results, only co-culture of H1437 + hDFs injected in the lungs significantly enhanced in vivo tumor growth. However, co-culture of H1650 with fibroblasts did not result in altered tumor growth in vivo.

Conclusions: Altogether, we established a 3D model with co-culture of NSCLC tumor cell aggregates and fibroblasts that, depending on the pair used, presented reduced sensitivity to standard of care drugs, better reflecting the clinical observations.

Legal entity responsible for the study: ibET/ITQB-UNL, AbbVie and Oncotest

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Tactics of surgical treatment of tumors of the sacrum

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Background: Tumor lesions of the sacrum are relatively rare and account for 1.7% of all spinal tumors. Tumors of this localization are usually detected when the tumor reaches a significant size and causes gross neurologic disorders and impaired pelvic organs. Radicality of removal of tumors of the sacrum depends on the involvement of the cauda equina, pelvic organs and vascular structures in the process.

Methods: The study involved 13 patients TMA clinic on the basis of the Department of Traumatology, Orthopedics, Neurosurgery with GPH No2 from 2011 to 2016. There were 6 women, 7 men. Age category ranged from 17 to 50 years. 1-stage: Holographic selective angiography by Seldinger’s method of small pelvic vessels with subsequent embolization of “feeding” tumor vessels. In addition, the anatomical features of the arteries are determined taking into account the localization of the tumor process, which is important in the operation. 2-stage: After preoperative embolization, three patients underwent hemisakrumectomy with VS3-VS5, and three patients underwent VS1-VS3 sacrectomy. In this case, patients were additionally stabilized by TPF systems among 13 patients during follow-up.

Results: In 2 cases during surgery, the tumor was intimately soldered to the roots of the horse’s tail and their isolation led to traumatization of the horse’s tail, resulting in a postoperative delay in urine and stool. These violations were resolved within 2 months. In 4 patients with tumoroma S1, S2, S3 spine, spine decompression was performed. In these cases complications from the pelvic organs were not observed due to the presence of a cross innervation. In 2 patients, because of the duration of the operation, supraposition of the operating wound was noted with subsequent secondary healing. There were no lethal outcomes among 13 patients during follow.

Conclusions: The tactics of surgical treatment of sacral tumors, including the preliminary embolization of “feeding” arteries with subsequent radical removal of volume formation, reduces the risk of intraoperative complications, and also allows to remove the tumor totally, which in turn prevents its recurrence.

Legal entity responsible for the study: Traumatology Department

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Background: Antibodies targeting the PD-1 pathway have shown durable clinical benefit in multiple cancers. In the KN028 trial, the antitumor activity and safety of pembrolizumab were investigated in 20 solid tumors. Associations between PD-L1 expression and a T-cell infiltrated GEP with response to anti-PD-1 therapy were also evaluated.

Methods: KN028 is a nonrandomized, phase 1b multicenter trial in patients with PD-L1 positive (≥5%), modified proportion score or interface pattern, QualTek IHC) advanced solid tumors treated with pembrolizumab 10 mg/kg Q2W for ≥2 or until confirmed progression/unacceptable toxicity, death or withdrawal of consent. An interim analysis was performed at 24 patients. In addition, pembrolizumab was compared to current standard of care with available tumor DNA that were finally treated by EGFR-TKI. ddPCR was performed with QX200 system (Bio-RAD, Hercules, USA). All samples were tested in duplicate. Colon cancers DNA were used as negative controls.

Results: ddPCR-identified a T790M mutation in 23/256 specimens (9%). T790M mutation was not correlated with a specific type of mutation (exon 18, 19, 20 or 21). T790M positive and T790M negative populations were not different for clinical baseline characteristics. In a Cox model, a lower OS was associated with T790M mutation (p = 0.02). In cases of rapid progression, OS (< 2 months) in patients with T790M mutations (exon 19, 20 or 21) was the same whether they were treated by EGFR-TKI or by pembrolizumab (p = 0.1, log-rank).

Conclusions: Pembrolizumab demonstrated favorable responses and manageable toxicity in the majority of the tumor types in KN028. Both PD-L1 and GEP score were predictive of clinical response, suggesting the utility of these biomarkers in selecting patients for immunotherapy and other novel therapies across a wide spectrum of tumor histologies.


Legal entity responsible for the study: Merck & Co., Inc., Kenilworth, NJ USA.

Funding: Merck & Co., Inc., Kenilworth, NJ USA.

Biomarker prevalence study and phase I trial of afatinib in children with malignant tumours

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Background: Dysregulation of the ErbB pathway may play a role in the development of paediatric neuroectodermal and mesenchymal tumours, suggesting that afatinib, an irreversible ErbB family blocker, could be an effective treatment. A biomarker study explores the tumor expression of angiogenesis-related genes as potential markers of anti-VEGF2 response. Methods: Through an observational prospective study carried by the Spanish Oncology Genitourinary Group (SOUGG) FFPE tumor samples were collected from 135 RCC patients. A NanoString® Custom CodeSets (NanoString Technologies) was designed to measure the expression of a selected set of genes involved in angiogenesis (n = 23), immune response (n = 5) and RCC mutational landscape (n = 4), together with 4 housekeeping genes. This technology was successfully applied to 135 primary tumours (81% clear cell histology), 4 metastasis, and 10 normal kidney tissues from patients treated with anti-VEGF2 therapy. The association between the expression of the genes and PFS and OS was analyzed through Cox-regression. Data provided correspond to multivariable analyses adjusted for MSKCC, prognosis group, RCC histology and age.

Results: The 135 patients studied had been treated with sunitinib (91%), pazopanib (7%), and sorafenib (1%), most in first line (98%) and the median PFS was 21.0 months (95%CI = 14.5-27.9). The strongest associations found corresponded to VEGFC, VEGFA, PENGRA and FGFR2. The median expression of these genes in the tumors was 28, 1075, 14 and 25 counts, respectively. High expression of VEGF2 was associated with poor OS (HR = 4.15, 95%CI = 1.47-11.59, P = 0.0098). FGFR2 and FGFR2 were associated with poor PFS (P = 0.01 and 0.012, respectively). Regarding OS, high expression of VEGF2 was associated with poor OS (HR = 6.18, 95%CI = 2.03-18.77; P = 0.0013). No significant associations were found for other genes.

Conclusions: We propose that the basal tumor expression of VEGF2 isosforms influences the survival of the patients treated with anti-VEGF2 drugs.

Legal entity responsible for the study: Spanish Oncology Genitourinary Group (SOUGG)

Funding: Spanish Oncology Genitourinary Group (SOUGG)

Disclosure: All authors have declared no conflicts of interest.
that may lead to skipping of exon 4 and an in-frame deletion existing a frameshift muta-
tion. Multiple reversion mutations were observed in 2 cases. Only 1/7 cases also showed disruption of BRCA1/2.

Conclusions: In addition to the commonly sequenced genes BRCA1/2, PALB2 muta-
tion can lead to homologous recombination deficiency. As with BRCA, the acquisition of additional mutations predicted to restore at least some PALB2 function and thus po-
tentially confer resistance to therapies dependent on HRD, can be observed in tumors such as breast, ovarian, and prostate carcinomas. CGP is a valuable tool to identify clinically significant, albeit rare, primary PALB2 mutations in BRCA-negative tumors as well as acquired secondary resistance mutations in patients who progress on Pt and PARP inhibitor based therapies.

Legal entity responsible for the study: Foundation Medicine

Funding: Foundation Medicine


90P Pan-cancer genomic analysis of MS-H tumors reveals commonly altered pathways

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Background: Microsatellite instability (MSI) is a hallmark of mismatch repair (MMR) deficiency and can be attributed to alterations in MMR-related genes including MSH2, MLH1, MSH6, and PMS2. Although alterations in PI3K pathway genes have been reported in MSI-H (MSI-H) colorectal carcinoma (CRC), a comprehensive enrichment analysis of the genomic landscape in MSI-H and MSI-stable (MSI-S) populations across tumor types is lacking. To better understand the molecular signatures of MSI-H tumors and investigate new avenues for therapeutic opportunities, we sought to define the genomic landscape of MSI-H tumors across cancer types.

Methods: Comprehensive genomic profiling of 395 cancer-related genes, including MSI status, was performed on ~70,000 tumors. To identify potential driver alterations enriched in MSI-H tumors, variants in regions likely to be affected by polymerase slippage were excluded.

Results: As expected, alterations in MSH2, MLH1, MSH6, and PMS2 as well as MMR deficiency variants were enriched in MSI-H specimens regardless of tumor type. We confirmed that variants in PI3K genes were enriched in MSI-H tumors in CRC. Importantly, this was observed across all MSI-H tumors, with 57% of pan-solid MSI-H tumors harboring a PI3K pathway variant compared to 24% of MSS tumors. WNT pathway variants were also enriched specifically in MSI-H tumors, except for CRC, in which frequent APC variants in MSS resulted in WNT enrichment in MSS tumors. Together, 84% of MSI-H tumors have at least one PI3K or WNT pathway variant (compared to 48% of MSS samples). Finally, although ERBB2 alterations occur in both MSS and MSI-H tumors, we found that ERBB2 amplifications occur nearly exclu-
sively in MSS tumors, while ERBB2 nonsense mutations are enriched in MSI-H tumors.

Conclusions: The genomic landscapes of MSI-H and MSS tumors suggest that they ac-
quire alterations in distinct pathways. MSI-H tumors appear to share signaling pathway alterations across diseases, suggesting that MSI-H tumors may be more molecularly similar to one another than they are to MSS tumors of the same disease histology. These data may provide new avenues for exploration of targeted therapies in MSI-H tumors.

Legal entity responsible for the study: Foundation Medicine Inc.

Funding: Foundation Medicine Inc.


90P Molecular feature and clinical use development of gene expression profile “TP53 signature” in early stage breast cancer

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Background: There have been reported many gene expression profile which can predict prognosis of early stage breast cancer. We have reported the TP53 signature which can predict dysfunction caused by TP53 gene mutation in transcription level, and the status defined by TP53 signature can predict more accurate prognosis of early stage breast cancer compared to the status defined by TP53 DNA sequence. Recently, TP53 signature was reported as robust predictor of early stage breast cancer by an analysis (BMC Cancer.2015). The aim of this study is to make clear the molecular feature of poor prog-
nosis group diagnosed by TP53 signature and to make easy and quick diagnostic kit which can be used in clinical situation.

Methods: We have done RNA seq analysis using Hiseq2500 (Illumina) and reanalyzed TCGA data of breast cancer to make clear molecular feature of poor prognosis group defined by TP53 signature. We made simple diagnostic kit using nCounter (Nanostring technology). Using this simple diagnostic kit, we diagnosed 234 breast cancer sample as TP53 signature mutant or TP53 signature wild, and we proved robust prediction power of TP53 signature for early stage breast cancer. We used RNA-seq data to compare pre-
diction power of TP53 signature to Mammaprint, OncotypeDX, TP53 structural mutation.

Results: TP53 signature mutant group have structural mutation in genes, including BRCA1, BRCA2, RB1 except for TP53, which function is gene repair. In addition, TP53 signature group showed high expression of PD-L1, high mutation burden and high copy number alternation. Analysis of 190 stage I-II breast cancer patients shows TP53 signature by simple diagnostic kit using nCounter has strong prediction power compare to Mammaprint, OncotypeDX, TP53 structural mutation, and clinical efficacy.

Conclusions: We have developed TP53 signature as diagnostic system for early stage breast cancer which is useful in clinical situation. Poor prognosis group diagnosed by TP53 signature shows molecular features which overlap good response marker of immune-check point inhibitors.

Legal entity responsible for the study: Japan

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Low expression of miR-20a-5p predicts benefit to bevacizumab in metastatic breast cancer patients treated within the TANIA trial

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Background: Biomarkers predicting response to a bevacizumab containing therapy in metastatic breast cancer (MBC) are of urgent need. MicroRNAs (miRNAs) are involved in regulation of angiogenesis and development of treatment resistance and could therefore provide predictive information.

Methods: Profiling of 754 miRNAs was performed in FEPE tumor samples from 58 MBC patients who received bevacizumab-containing first-line treatment (learning set). Based on median PFS in patients who received bevacizumab, the median PFS was divided into responders (R) and non-responders (NR). Differentially expressed miRNAs between R and NR were selected and validated in a cohort of 57 patients treated with first-line chemotherapy without bevacizumab (control set), to exclude miRNAs providing prognostic information only. In the learning set a multivariate analysis including clinical and pathological information was performed. miRNAs significantly associated in the learning set were evaluated in the patients treated within the TANIA phase III trial randomizing between chemotherapy plus bevacizumab and chemotherapy alone for two consecutive treatment lines in patients pretreated with bevacizumab in first-line.

Results: Low expression of five miRNAs (miR-9-5p, miR-20a-5p, miR-21-5p, miR-210-3p, and miR-224-5p) was significantly associated with longer PFS in the learning set. For miR-20a-5p (P < 0.035) and miR-21-5p (P = 0.004) this association remained significant in the multivariate analysis. In the control set no correlation between the expression of those five miRNAs and PFS was seen. In tumor samples from the TANIA trial, low expression of miR-20a-5p was also significantly associated with longer second-line PFS and longer OS in the bevacizumab arm (HR 0.66, 95% CI 0.37-0.89; P = 0.012 and HR 0.54, 95% CI 0.32-0.83; P = 0.007, respectively) but not in the chemotherapy only arm (HR 0.73, 95% CI 0.48-1.09; P = 0.119 and HR 1.01 95% CI 0.63-1.62; P = 0.964, respectively). For miR-21-5p no significant association with PFS or OS in both treatment arms was observed.

Conclusions: miR-20a-5p expression in breast cancer tissue showed a promising predictive for identifying patients deriving greater benefit from bevacizumab-containing therapy.

Legal entity responsible for the study: Richard Greil for the translational research project, Roche for the TANIA trial

Funding: Roche

Disclosure: S.P.P. Gampnerrieder, G. Rinnerthaler, A. Egle, R. Greil: Advisory role, speakers' honorarium, travel grants, research funding (no personal payment) from Roche. C. Monzo Fuentes: Travel grants from Roche. C. Hufnagl, C. Häuser-Kronberger: Travel grants, research funding (no personal payment) from Roche. All other authors have declared no conflicts of interest.

Characterization of a novel tumor-suppressor gene CHL1 at 3p26.3 in esophageal squamous cell carcinoma

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Background: The major histological subtype of esophageal cancer, esophageal squamous cell carcinoma (ESCC), is one of the most common cancers and has been ranked as the sixth leading cause of cancer-related deaths in the world. Using human genome U133 Plus 2.0 GeneChip, we identified gene down-regulation of Cell adhesion molecule L1 like (CHL1) located at 3p26.3 in ESCC. We analysed its down-regulated expression, biological effects and prognostic significance in ESCC.

Methods: To determine whether the down-regulation of CHL1 was associated with aberrant methylation. Methylation-specific PCR (MSP) was performed in ESCCs and their corresponding non-tumor tissues, as well as ESCC cell lines. Loss of heterozygosity status of CHL1 was evaluated by fluorescence in situ hybridization (FISH). The effects of CHL1 re-expression or knockdown were determined in proliferation, invasion and metastasis assay. CHL1 target genes and related pathways were identified by protein mass spectrometry, co-immunoprecipitation (Co-IP), immunofluorescence (IF) and western-blot. Clinical impact of CHL1 down-regulated expression was assessed in 208 patients with ESCC.

Results: The results showed that down-regulation of CHL1 was significantly associated with allelic loss (14:21) and promoter methylation (192:0.05) in 39 pairs of ESCCs and their corresponding non-tumor tissues by using MSP and FISH. Bioinformatic investigation of CHL1 revealed that CHL1 significantly decreased cell proliferation, G1-S cell cycle arrest and induced apoptosis (P < 0.05) in Hs108 T cells and promoted xenograft tumor growth as well as lymph node metastasis in vivo. The anti-proliferation effect by CHL1 was mediated through inducing cell cycle arrest at G1/S checkpoint by down-regulation of p21 and up-regulation of cyclin D1; the inhibiting metastasis role was supported by the G1/S-phase transition and E-cadherin up-regulation, which was the result of recruitment Merlin to cell surface expression by CHL1. After a median follow-up of 48.23 months, multivariate analysis revealed that patients with CHL1 protein down-expression had a significant decrease in overall survival. Kaplan-Meier survival curves showed that CHL1 down-regulated expression was significantly associated with shorter survival in patients with ESCC.

Conclusions: CHL1 plays a pivotal tumor suppressive role in ESCC; its down-regulated expression is an independent prognostic factor of patient with ESCC.

Legal entity responsible for the study: Henan Cancer Hospital

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The role of vitamin D receptor polymorphisms in predicting response to therapy in non-muscle invasive bladder carcinoma

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Background: Clinico-pathological factors predicting for response to Bacillus- Calmette Guerin (BCG) treatment for non-muscle invasive bladder carcinoma (NMIBC) are well defined but there is a paucity of data on genetic factors. Vitamin D has been found to have immunomodulatory effects in pre-clinical bladder cancer studies. Various single nucleotide polymorphisms of the Vitamin D Receptor (VDR) gene has also been found to be associated with response to treatment for mycobacterium. In this study, we evaluated the predictive role of VDR single nucleotide polymorphisms (SNP) in patients with NMIBC in assessing BCG immunotherapy outcome.

Methods: Peripheral blood DNA was prospectively obtained from 140 evaluable NMIBC patients who underwent post-transurethral resection transurethral regimes of BCG or BCG with interferon alpha. 3 VDR SNPs commonly implicated in susceptibility to tuberculosis infections were evaluated using high resolution melt (HRM) analysis followed by DNA sequencing. Kaplan-Meier together with Log-Rank test and Cox regression methods were used to analyze the data.

Results: Genotype frequencies were similar between the NMIBC patients and controls in accordance to the Hardy Weinberg equilibrium. Mean follow up time was 91.9 months. Overall mean time to recurrence and progression was 25.8 months and 47.0 months respectively. Kaplan-Meier analysis indicate that individuals carrying the VDR genotype rs154410 A/G were significantly associated with lower recurrence-free survival rates after BCG therapy (p = 0.007). The VDR rs154410 “A” allele frequency was found to be higher in patients with bladder cancer recurrences (p = 0.011). No association of VDR genotypes with progression-free survival was found.

Conclusions: Our findings suggest that polymorphisms in the VDR gene correlate with response to BCG therapy in NMIBC patients and further work should be performed to evaluate their utility as predictive markers of response to BCG immunotherapy.

Legal entity responsible for the study: National Healthcare group Domain Specific Review Board

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Disclosure: All authors have declared no conflicts of interest.

Gene signatures as potential predictive markers of response to neoadjuvant chemotherapy in ER+/HER2+ breast cancer patients

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Background: Chemotherapy (CT) combined with anti-HER2 drugs (H) is the treatment of choice for HER2+ early breast cancer (BC) patients (pts). However HER2+ tumors are clinically and biologically heterogeneous, and treatment response largely varies according to ER status. Predictive biomarkers are urgently needed in this context. We have recently developed a meta-dataset of clinical trials of neoadjuvant CT+/HER2+/Hi nE R breast cancer patients annotated for gene expression, hormone receptor status and pathological complete response (pCR) rates. We have shown that a gene-signature (GS) of ER+/HER2+ pCR was significantly associated with lower recurrence-free survival rates after BCG therapy (p = 0.007). The VDR rs154410 “A” allele frequency was found to be higher in patients with bladder cancer recurrences (p = 0.011). No association of VDR genotypes with progression-free survival was found.

Conclusions: Our findings suggest that polymorphisms in the VDR gene correlate with response to BCG therapy in NMIBC patients and further work should be performed to evaluate their utility as predictive markers of response to BCG immunotherapy.

Legal entity responsible for the study: National Healthcare group Domain Specific Review Board

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Neoadjuvant chemotherapy in ER+/H##+ breast cancer patients
In pts treated with CT + H (n = 117) only the HER2+ ampiclon GS significantly correlated with PCR (p<0.042). Ribisg showed a similar trend in both these subgroups (p: 0.078 and 0.104, respectively) The immune GSs and PAM50 were not associated with PCR, independent of treatment received.

Conclusions: Ribisg and HER2+ ampclon GS are strongly associated with PCR in ER+/HER2+ tumors unselected for treatment. These results support the potential use of such GSs as predictive markers of response to CT +/- H in ER-+/HER2+ BC pts. Validation studies are warranted.

Legal entity responsible for the study: Angelo Di Leo

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Disclosure: A. Di Leo: Consultant/Advisory Board: Novartis, Pfizer, Lilly. All other authors have declared no conflicts of interest.

96P

Predictive biomarkers for adjuvant therapy in gastric adenocarcinoma

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Background: Gastric cancer is a common and lethal malignancy, killing over 700,000 people worldwide. Poor outcomes are mainly due to high rate of recurrences and at least 5-10 years after surgery. This TMA slide was stained with Feulgen-thionin and imaged using a high-resolution Imaging system. Automated segmentation of cell nuclei followed by machine learning techniques allowed us to develop a computational prediction tool that can differentiate the tumour epithelial nuclei from the stromal components, sparing the rest from unnecessary exposure to toxic and expensive adjuvant therapies.

Methods: We tested our algorithm on a set of 172 TMA cores samples, coming from 95 patients with primary gastric adenocarcinoma. The percentage of tumour epithelial nuclei is an indicator of the aggressiveness of the tumour.

Results: Forward stepwise Linear Discriminant analysis selected 6 features that, combined linearly, gave the best discrimination between nuclei from alive patients specimens and nuclei from deceased patients specimens. Patient LDO score was defined as the sum of percentage of cell nuclei with a high cell LDO. LDO algorithm correctly classified 82.1% patients, with a specificity of 79% and a sensitivity of 88%. Furthermore, individual patients with a high LDO score had a 9x fold increase in relative risk of death. In the multivariate Cox regression model, LDOs, Node status and Tumor Grade were all significant predictors of cancer death.

Conclusions: This data suggests that LDO could be used to identify patients more likely to have an aggressive disease and thus select a candidate for more aggressive or novel adjuvant therapies. Legal entity responsible for the study: Martial Guillaud

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98P

Telomere associated variables and their potential in CLL prognosis

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Background: The molecular mechanisms that determine disease progression and evolution in CLL are not completely known. Telomeres are usually short in CLL and their attrition may contribute to disease evolution. In addition, telomerase activity (TA) levels have also been associated with prognosis and response to treatment. In order to integrate telomere associated variables (TAV) in CLL disease management further studies with robust methodology are required.

Methods: Purified peripheral CD19 (+) B-cells from 19 healthy donors and 42 CLLs in different stages of disease were obtained from the National Bank of DNA (Salamanc, Spain). Samples were tested to determine full telomere length (TL) distribution and including percentage of short telomeres by a high throughput quantitative fluorescence in situ hybridization (HTQ-FISH) technique. TA by Quantitative Telomere Repeat Amplification Protocol (Q-TRAP) was also quantified. Full statistical analysis of the results in the context of the clinical history of the patients was performed.

Results: Data from the pilot, retrospective study established strong correlations between key TAV and the severity of the disease. Overall, TL was shorter and TA presented higher values compared to normal age-matched subjects. Interestingly, longer TL was observed for all CLL patients with somatic hyper-mutation (SHM) that in turn, was associated with better prognosis. Concomitantly, TA was elevated in those patients associated with no SHM and was linked to poor response to treatment and negative prognosis. The percentage of short telomeres was significantly higher for SHM /Crai III and IV cases.

Conclusions: The use of reliable technologies to measure TAV should be integrated during early diagnostic in CLL to enhance the ability to predict disease evolution. This will require larger, prospective, longitudinal clinical studies.

Legal entity responsible for the study: Life Length S.L.

Funding: Life Length S.L.


97P

Large-scale DNA organization is a prognostic marker of breast cancer survival

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Background: Breast cancer is the leading cause of cancer-related deaths among women worldwide. Current clinicopathological parameters only partially encompass and predict biological diversity and therefore limit our ability to make informed treatment decisions and predict outcomes. The successful future of oncology will rely on our ability to correctly select patients who would benefit from chemotherapy or benefit from treatment intensification, and spare the rest from unnecessary exposure to toxic and expensive therapies. Tumour biology and prognostic markers may be the key to achieving the above goal. We investigated whether changes in Large scale DNA organisation (LDO) of tumour epithelial nuclei is an indicator of the aggressiveness of the tumour.

Methods: We tested our algorithm on a set of 172 TMA cores samples, coming from 95 breast cancer patients. Thirty five patients died of breast cancer and 60 were still alive 9 years after surgery. This TMA slide was stained with Feulgen-thionin and imaged using an high-resolution Imaging system. Automated segmentation of cell nuclei followed by manual selection of intact, in-focus nuclei resulted in an average of 50 cell nuclei per sample. Approximately 60 features measuring Large-scale DNA organization were calculated.

Results: From the present study we recorded clinical data from 57 mBC patients, and selected two (4 + 4) PFS extreme groups for the analysis of the miRNome. Three miRNAs were used for normalization (U6, 191-5p and 103-a-3p). miRNAs for model construction were selected by differential expression between the two groups. Candidates were
measured in the remaining 49 cases, and stepwise based Akaike criterion was used for profile generation. Additionally, integrative miRNA and mRNA analyses were done to reveal markers and pathways with potential clinical impact.

Results: We selected two groups of patients with extreme differences on PFS (2.48 ± 1.85 vs 5.53 ± 2.03 months) for their miRNA study. The expression profiles of miRNAs in both groups were highly correlated, except for 13 miRNAs where statistical differences arose. These miRNAs were selected as candidates for profile generation on the 49 additional cases, and a combination of five of them (miR-362-3p, miR-150-5p, miR-671-3p, miR-744-3p and miR-941) was able to accurately discriminate two PFS groups. Additionally, Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses on miRNA possible target genes revealed interesting pathways to explore in these patients, such as cellular adhesion.

Conclusions: By combining experimental approaches and computational biology, we have identified candidate markers of outcome for bevacizumab-containing therapy. The five miRNAs included in the prognostic profile and cellular adhesion related genes should be explored as potential biomarkers.

Legal entity responsible for the study: Fundación para la Investigación del Hospital Universitario La Paz

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Disclosure: All authors have declared no conflicts of interest.

100P Biomarkers of immune therapy in CUP

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Background: Carcinoma of unknown primary (CUP) accounts for approximately 3% of all malignancies. Identification of common cancer pathway alterations (hallmarks of cancer) in diverse cancer lineages offers a rationale for search for biomarkers of targeted therapies in patients with CUP. Avoiding immune destruction is a more recently recognized common characteristic and biomarkers associated with immune checkpoint blockade were explored in this study.

Methods: 392 cases of CUP were tested with NextSeq platform with a 592-gene panel. Tumor mutational load (TML) was calculated using only somatic nonsynonymous missense mutations; microsatellite instability (MSI) was evaluated with NGS by using MRC. Tumor expression of PD-L1 was assessed using only monoclonal antibodies (NAT105 antibody) and PD-1 TILs (NAT105 antibody) All tests were done in a CLIA-certified lab.

Results: Average patient’s age was 62.4 years; 52% were female. TML high was seen in 12.2% (48/392) tumors using a cutoff of 17 mutations/Mb. MSI-high was detected in 10/392 (2.6%) of tumors. A total of 70 different genes were found mutated with the incidence ranging from 0.3% to 54%; the most frequent were TP53 (53.5%), KRAS (21.5%) and ARID1A (14.6%). Additional notable targetable mutations include PIK3CA (13.1%), CDKN2A (8.1%), PTK3 (4.5%), BRAF (4.1%), ATM (3.3%), NOTCH1 (2.4%) and ERBB2 (1.5%). Targetable gene fusions included FGFR2 fusions (N = 2), RET (N = 1), RAF1 (N = 1). Tumors with fusions identified carry a lower TML (average 5.9) than the complete cohort (11.7, p = 0.001) with no significant independent prognostic factor for DFS in resectable PDAC patients, and it was demonstrated that, among a series of cytokines, IL4 is the most significant independent prognostic factor for DFS in resectable PDAC patients, and it could be useful to select patients with high risk of early recurrence who may avoid an unnecessary resection.

Legal entity responsible for the study: University of Verona

Funding: Associazione Italiana per la Ricerca sul Cancro (AIRC)

Disclosure: All authors have declared no conflicts of interest.

102P Analytic validation of a next generation sequencing assay to identify tumor mutational burden from blood (bTMB) to support investigation of an anti-PD-L1 agent, atezolizumab, in a first line non-small cell lung cancer trial (BFAST)

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Background: Recent data suggest that analysis of tumor mutational burden (TMB), a measure of tumor neo-antigenicity derived from tissue biopsies, has shown clinical utility in predicting outcomes for patients treated with anti-PD1/PD1 therapies across a range of tumor types. Unfortunately, such analyses require quality tumor tissue that in many cases is not available for patients diagnosed in the metastatic setting. As such, there exists a significant unmet medical need for orthogonal diagnostic approaches that enable the analysis of TMB in patient samples without requiring tumor tissue. Herein, we describe the development of an assay to identify TMB from the circulating tumor DNA derived from blood (bTMB), and the analytical validation (AV) that supports its application in a phase III clinical trial in NSCLC patients comparing the anti-PD-L1 agent, atezolizumab, against standard of care platinum-based doublet chemotherapy (BFAST).

Methods: The bTMB assay delivers a count of somatic base substitutions down to 0.5% allele frequency across 394 genes from as little as 1% tumor content in a cell-free DNA (cfDNA) sample. AV focused on establishing accuracy and precision, as well as the limit of circulating tumor DNA required to make precise and reliable bTMB calls. Accuracy of the two different bTMB cutoffs being evaluated in BFAST was established against an orthogonal validated TMB platform. Precision was evaluated by comparing the reproducibility of bTMB calls across replicate samples.

Results: The average PPA, PNP and PPV across both bTMB cutoffs was 95%, 100% and 100%, respectively. The average precision was 96%, with a coefficient of variation of 17% across all replicates. The assay limit of detection was defined as 1% tumor content at least 20 ng of cfDNA.

Conclusions: We have developed and analytically validated a blood-based assay to determine bTMB with high accuracy and precision from as little as 1% tumor content in 20 ng of cfDNA. Clinical validation of bTMB will be established in a prospective, randomized phase III clinical trial, BFAST, with a primary endpoint of progression free survival.

Legal entity responsible for the study: Foundation Medicine, Inc.

Funding: Genentech, Inc.

Comparison of continuous measures across diagnostic PD-L1 assays using image analysis

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Background: Tumour programmed cell death ligand-1 (PD-L1) expression is a key biomarker in identifying patients who may have an enhanced response to non-small cell lung cancer treatment using anti-PD-1 (e.g. nivolumab and pembrolizumab) or anti-PD-L1 (e.g. atezolizumab and durvalumab). Each treatment is currently used in conjunction with an individual PD-L1 diagnostic immunohistochemistry (IHC) assay and it is unclear whether immunolabelling parameters determined by pathologists are comparable across assays. We extended previous studies (Ratcliffe et al Clin Cancer Res 2017; Raciti et al ASCO-SETC 2017 [abstr 7]) by performing image analysis (IA) with a customised PD-L1 scoring solution to permit a quantitative comparison of the 4 PD-L1 methods.

Methods: We developed an IA scoring algorithm that enabled us to quantify the percentage of positive tumour cells on a whole slide image for 4 PD-L1 assays (Ventana SP263, Ventana SP142, Dako 28-8, Dako 22C3). The analysis was applied to 473 commercially available NSCLC cases (180 cases with SP263). We co-registered the consecutive slides per case and harmonised tumour and exclusion annotations to ensure that readouts of identical areas were compared per case.

Results: In agreement with previous reports, IA results showed concordance between 3 assays, whereas the SP142 assay was discordant. Moreover, high correlation was observed between IA results and pathologist ratting. This correlation could be further improved by matching the information the pathologist received to the same information used in the IA solution: blinding against the assay, scoring on digital scans and masking of non-comparable image regions. The remaining differences represent the differing sensitivity profiles of the assay protocols.

Conclusions: This study confirms that these image analysis solutions can be used to quantify the status of tumours in a more objective and standardised manner, and can be used to determine the relative efficacy of different diagnostic assays in a more objective manner: these findings may have important implications for future studies, particularly in combination with clinical trial data.

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Pharmacokinetics (PK) and pharmacodynamics (PD) of a novel carcinoembryonic antigen (CEA) T-cell bispecific antibody (CEA-CD3 TCB) for the treatment of CEA-positive solid tumors

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Background: CEA-CD3 TCB (RG7802) is a novel T-cell bispecific antibody targeting CEA on tumor cells and CD3e on T cells. In mouse models, CEA-CD3 TCB in an adoptive anti-tumor activity, leads to increased intratumoral T cell infiltration and activation and up-regulates the PD-1/PD-1 pathway.

Methods: Biodistribution was assessed in mice using SPECT/CT. Patient (pt) samples were from 2 dose-escalation studies in CEA-positive solid tumors. Study 1 (S1): single agent weekly (qw) (0.052-600 mg IV, n = 80), and Study 2 (S2): CEA-CD3 TCB qw (3-160 mg IV) plus atezolizumab 1200 mg qw (n = 46). Analytics: [CEA-CD3 TCB]—bifunctional PK assay; antidrug antibodies—ELISA; immunomodulatory in peripheral blood (PB)—flow cytometry (FCM), in baseline (BL) and on-treatment (OT; week 7) biopsies by immunohistochemistry and FCM; plasma cytokines—multiplex assay; PD-L1—SP142 assay.

Results: In mice, CEA-CD3 TCB preferentially accumulated in CEA-positive tumors. CEA-CD3 TCB showed near-linear PK in both studies (S1: 33; S2: 28). In pts with matched BL and OT biopsies, 7/10 CRC pts treated with ≥ 60 mg of CEA-CD3 TCB in S1 had > 2.4-fold increase in CDB T cells, which did not correlate with RECIST response. In S2, 2/3 CRC pts receiving ≥ 80 mg of CEA-CD3 TCB (with RECIST reduction ≥ 25%), showed > 8-fold increase in CDB/K6 T cells. SUVmax decrease (FDG-PET) correlated with BSL levels of C4D-OX40 and CDB-PDI in S1 and CDB-OX40 in S2. In PR at week 4, a 4-6 fold expansion of activated CDB T cells (HLA-DR/Kit) but not C4D, was detected in most pts at doses ≥ 60 mg (S1: 24; S2: 29). In most pts, increases in IL-6 were seen after the first TCB infusion and in fewer cases after the second/third infusion in both studies (S1: 62; S2: 53).

Conclusions: On-treatment increases in intratumoral CDB T cells consistent with the mechanism of action and support that CEA-CD3 TCB is the first tumor-targeted T cell bispecific showing biological activity. The activation level of intratumoral T cells at BL could be a predictive biomarker of response. In preclinical models, tumor targeting has been demonstrated. Updated data will be presented. Clinical data are reported separately.

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Baseline gut microbiota in metastatic melanoma patients treated with ipilimumab: Relation with clinical response and colitis

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Background: It is now demonstrated that gut microbiota composition has a determining influence not only on inflammatory bowel diseases but also on the immunological status of healthy individuals as well as in patients with cancer. We explored the potential role of baseline gut microbiota in anti-tumor response and in intestinal toxicity of patients with metastatic melanoma treated with anti-CTLA4 mAb ipilimumab. Moreover we explored how the composition of gut microbiota could influence not only local gut-immunity but also distant sites such as anti-tumor immunity.

Methods: Fecal microbiota compositions were prospectively assessed at baseline and before each ipilimumab infusion, using 16S rRNA gene sequencing. Patients were further clustered based on microbiota patterns. Peripheral blood lymphocytes immunophenotypes were studied in parallel.

Results: A distinct baseline gut microbiota composition was associated with both clinical response and colitis. As compared to patients whose baseline microbiota was driven by Bacteroides (Cluster B), patients whose baseline microbiota was enriched with Firmicutes (Cluster A) had longer progression-free survival and overall survival. Most of the baseline colitis-associated phenotypes were related to Firmicutes, whereas no colitis related phenotypes were assigned to Bacteroides. A low proportion of peripheral blood regulatory T cells was associated with Cluster A, long-term clinical benefit and colitis. Ipilimumab led to a higher Inducible T cell CDStimulator induction on CD4+ T cells and to a higher increase in serum CD52 in patients who belonged to Cluster A.

Conclusions: Baseline gut microbiota enriched with Firmicutes is associated with beneficial clinical response to ipilimumab and more frequent occurrences of ipilimumab-induced colitis.

Clinical trial identification: G017 study: SC12-018; ID-RCB-2012-A01496-37

Legal entity responsible for the study: Coordination: Franch Carbonnel (AP-HP)
Funding: This study was funded by academic groups only: 1- Gustave Roussy Cancer Campus 2- Fondation Gustave Roussy 3- Direction Générale de l’Offre de Soins (DGOS; GOLD TRANSAL 12-174). 4- Institut National du Cancer (INCa; GOLD 2012-062) 5- Cancéropole 2012-1. RT-14 OT-01 6- SIRIC SOCRATE (INCa DGOS INSERM 6043) 6- MMO program ANR-10BBHU-0001


Conclusions: MSI tumours are heterogeneous and can be stratified by virtue of differentiation states (or cell-of-origin) and different immune phenotypes. With further studies, this heterogeneity may help select MSI cancer patients for immune checkpoint combination therapies.

Legal entity responsible for the study: Anquraj Sadanandan

Funding: NHIR Biomedical Research Centre at the Royal Marsden Hospital and Institute of Cancer Research, London, UK; Cancer Research UK.

Disclosure: A. Sadanandan: Entitled to a share of royalties received by the licensor for a patent patent number PCT/IB2013/060416. Received research funding from Bristol-Myers Squibb for pancreatic cancer. All other authors have declared no conflicts of interest.

108P Characterisation of heterogeneity in microsatellite instable (MSI) tumours associated with distinct cell types and immune phenotypes

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Background: In the immunotherapy era, a better understanding of heterogeneity in MSI cancers is required. We evaluated gene expression profiles of MSI colorectal (CRC), gastric (GC) and endometrial cancer (EC) samples with our cell-of-origin signature (CRCcassigner), which is able to classify samples in differentiated (goblet-like; CMS3), differentiating (transit-amplifying – TA; CMS2) and less differentiated/mesenchymal (stem-like; CMS4 and inflammatory; CMS1) subtypes to identify whether MSI transcriptional heterogeneity exists.

Methods: Normalised RNAseq/microarrays gene expression profiles and microsatellite status were downloaded from TCGA. CRCcassigner classification of samples was performed using Pearson correlation. Samples with low classification confidence were classified as “mixed” subtype. Gene selection enrichment analysis (using published immune markers) and differential protein expression analysis (of PD-L1 from Cancer Proteome Atlas data) was performed by inflammatory and goblet-like MSI samples.

Results: The majority of MSI-H in all the 3 cancer types expressed the inflammatory profile. While in MSI-H CRC only two subtypes were present (inflammatory - 91% and goblet-like - 9%), 5 subtypes in MSI-H GC (inflammatory - 43%, goblet-like - 24%, stem-like - 21%, TA - 6%, enterocyte - 3%) and 4 subtypes in EC (inflammatory - 36%, stem-like - 36%, goblet-like - 14%, TA - 14%) were present. Infiltrative MSI tumours from all the three cancer types were significantly (p < 0.05) enriched for genes associated with checkpoint inhibition (PD-L1), HIC Class I, Type I interferon response and macrophages compared to goblet-like MSI tumours. On the other hand, goblet-like MSI cancer showed enrichment of B-cells.

Conclusions: MSI tumours are heterogeneous and can be stratified by virtue of differentiation states (or cell-of-origin) and different immune phenotypes. With further studies, this heterogeneity may help select MSI cancer patients for immune checkpoint combination therapies.

Legal entity responsible for the study: Anquraj Sadanandan

Funding: NIHR Biomedical Research Centre at the Royal Marsden Hospital and Institute of Cancer Research, London, UK; Cancer Research UK.

Disclosure: A. Sadanandan: Entitled to a share of royalties received by the licensor for a patent patent number PCT/IB2013/060416. Received research funding from Bristol-Myers Squibb for pancreatic cancer. All other authors have declared no conflicts of interest.
survival outcome. And we found patients with PD-L1 expression and high PLR had the worst prognosis. The 5-year DFS rates were 68.4% and 85.8% in high PLR + PD-L1 (+) group and low PLR + PD-L1 (-) group respectively (p = 0.002). The 5-year OS rates were 73.4% and 90.1%, respectively (p < 0.001).

Conclusions: High PLR are associated with poor DFS in breast cancer patients. PD-L1 expression combined with high PLR was associated with an aggressive clinical outcome. Further studies are needed to evaluate the predictive value of combination of PD-L1 and peripheral blood immune markers.

Legal entity responsible for the study: Shusen Wang

Funding: National Natural Science Foundation of China (81502302); Science and Technology Program of Guangdong Province (2014A020212384; 2016A020125079)

Disclosure: All authors have declared no conflicts of interest.

110P Prognostic and predictive value of lymphovascular invasion and lymph node status among breast cancer subtypes

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Background: Breast cancer subtype (BCS) and lymphovascular invasion (LVI) have both been independently demonstrated as prognostic factors. The objective of this investigation was to evaluate the prognostic power of LVI and lymph node status among BCs.

Methods: From an institutional database, 2017 women with a histopathologically confirmed diagnosis of breast cancer treated between January 2008 and December 2016 were consecutively selected for participation in this study.

Results: Of the 2017 patients with breast cancer in the BCs groups, the highest OS and RFS rates were observed in luminal A subtype (95.6% vs. 95.1%, respectively) and the lowest were observed in TN subtype (83.3% vs. 83.0%, respectively). There were significant differences in OS according to the LVI status within the luminal A, luminal B and luminal HER2 subtypes. There were also a significant difference in the RFS rate of the luminal A, luminal B, luminal HER2 and HER2 subgroup. Therefore, we inferred that there were stronger links with LVI and BCS with regard to OS and RFS rates.

Kaplan-Meier analysis showed that there were significant differences in the OS and RFS rates according to the LVI status among the BCS groups. There were significant differences in OS according to the LVI status in the distribution of the luminal A, luminal B, luminal HER2, and TN subtypes. There were also significant differences in the RFS rates among the luminal A, luminal B, luminal HER2, and HER2 subtypes. On multivariate analysis, after controlling for age, tumor size was independently associated with LVI and lymph node status among all BCs groups. There were significant differences in OS according to the status of lymph node-negative and LVI-positive in the luminal HER2 subtype, as well as lymph node-positive and LVI-positive in the TN subtype. There were also significant differences in RFS according to the status of lymph node-negative and LVI-positive in the luminal A subgroup.

Conclusions: LVI and lymph node status were important prognostic factor for OS and RFS among all BCs. In lymph node-negative breast cancer, luminal HER2 had greater predictive value for OS, whereas luminal A displayed greater predictability for RFS. In lymph node-positive breast cancer, the TN subtype had greater predictive value for OS.

Legal entity responsible for the study: Tri-Services General Hospital, National Defense Medical Center

Funding: None

Disclosure: All authors have declared no conflicts of interest.

111P PD-L1 expression in TNBC: A predictive biomarker of response to neoadjuvant chemotherapy

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Background: Immune system plays an important role in tumor surveillance and escape. Recently tumor infiltrating lymphocytes (TILs) have been proposed as a predictive biomarker for clinical outcome and pathological response (pR) after neoadjuvant (neoad) chemotherapy (CT) in breast cancer. PD-L1 is expressed in about 20% of TNBC, suggesting the possibility of being a therapeutic target for this subtype of cancer. Here we studied the association between PD-L1 expression and pR in TNBC.

Methods: We retrospectively reviewed medical records of 54 patients who had received neoad CT (RC for 4 cycles followed by Paclitaxel q21 for 4 cycles) between Jan 2008 and Dec 2016 at Policlinico Umberto I and San Giovanni Hospital of Rome. We performed IHC for CD20, CD5, CD45, CD8, CD68, N-CAM and PD-L1 (Ventana SP142 clone) in basal paraffin -embedded biopsies. PD-L1 expression on tumor cells was evaluated both qualitatively (membrane staining intensity 0 to 3+) and quantitatively (% of positive cells). The percentage of TILs positive for PD-L1 was also recorded. Statistical analysis was performed with T di Student test and z-test.

Results: We enrolled 54 pts (median age: 50 y; range 28-75) affected by TNBC: 51 ductal (94.4%), 2 metaplastic (3.7%), 1 lobular (1.9%). The clinical stage before neoad CT was as PLR: 12.9% CT1 (7 pts), 72.2% CT2 (39 pts), 7.9% CT3 (2 pts), 1.9% CT4 (1 pt) and 5.3% CTx (3 pts). 23 pts were cN1 (42.5%). After neoad CT 30 pts underwent mastectomy (55%) and 24 conservative surgery (45%). 19 pts (35%) showed pCR. No significant associations were found between pR and CD, TN, age, histotype and immunohistochemical parameters will be reported.

Conclusions: Basal PD-L1 expression on cancer cells was associated with a better pR in TNBC undergoing neoad CT. The introduction of anti PD-1/PD-L1 therapy in this setting of pts could lead to interesting results.

Legal entity responsible for the study: Sapienza University of Rome

Funding: None

Disclosure: P. Marchetti: Advisory board and meeting with Pfizer, Roche, Novartis, MSD, Bristol-Myers Squibb, Ipsen, AstraZeneca, Boehringer Ingelheim. All other authors have declared no conflicts of interest.

112P Pathological evaluation of tumor infiltrating lymphocytes and the benefit of nivolumab in advanced non-small cell lung cancer (NSCLC)

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Background: Assessment of tumor infiltrating lymphocytes (TIL) by pathologists using Hematoxylin-Eosin (H&E), has been described as a prognostic factor in resected NSCLC. We aimed to correlate TIL to the benefit from nivolumab in patients (pts) with treated advanced NSCLC.

Methods: Patients with advanced NSCLC treated with nivolumab, with biopsy available for evaluation, were included between November 2012 and February 2017 in two cancer centers. Patients characteristics and outcome were collected. The percentage of tumor infiltrating lymphocytes in the stroma was evaluated using H&E staining from archival pretreatment tumor tissue samples. Primary endpoint was to correlate TIL density with progression free survival (PFS).

Results: Out of ninety-eight patients included 60 (61%) pts were male, with median age of 61 years and 85 (89%) were smokers. Sixty three (73%) pts were PS 0-1. Sixty tumors (61%) were adenocarcinoma, 29 (30%) squamous and 9 (10%) other histologies. Among 83 tumors with known molecular profile, 22 (27%) were KRAS mutated 7 (8%) EGFR mutated, 11% ALK positive. The median treatment line was 3 (2-4). The median follow up was 8 months (95%CI 6-19). The median PFS was 2 m (95%CI 1-5). The ORR was for 16%. The median TIL density was 5% (2-15). TIL density >5% correlated with PFS in univariate and multivariate analysis (HR: 0.49 [0.28-0.82] p = 0.007 and HR: 0.51 [0.14-0.86] p = 0.040 respectively). TIL density >5% was also associated with better ORR (OR = 3.5, 95%CI 1.16-11.71, p = 0.04).

Conclusions: Pathological assessment of TIL allows an easy evaluation of immune infiltration in NSCLC and independently correlates PFS in NSCLC pts treated with nivolumab. Results from validation cohorts and combination with other morphological and immunohistochemical parameters will be reported.

Legal entity responsible for the study: Ikarah Garan

Funding: None

Disclosure: All authors have declared no conflicts of interest.

113P Could a systemic inflammation response index (SIRI) predict overall survival (OS) in metastatic pancreatic cancer (PC)?

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Background: Cancer-associated inflammation is a key molecular feature of PC and may affect the clinical course. The aim of this study was to evaluate the prognostic relevance of SIRI based on peripheral neutrophil, monocyte, and lymphocyte counts in metastatic PC and its association with the metastatic site.

Methods: Retrospective analysis of the medical records of patients with pathologically confirmed metastatic PC between January 2011 and December 2016. Patients were classified as having liver metastases (LM) or extraperitoneal metastases alone (EM). Associations with overall survival (OS) were analyzed using Cox proportional models.
Results: A total of 37 patients were included (47 men; median age 63). Median TTP was 4 months and median OS was 6 months. 29 patients (78%) had LM and 8 (22%) EM. 33 patients (89%) received CT; 13 (40%) Gemcitabine (GEM) plus Nab-Paclitaxel, 9 (27%) GEM in monotherapy, 7 (21%) GEM plus Erlotinib and 4 (12%) an Oxaliplatin doublet. Mean CA 19.9 levels in patients with LM were 199349 and with EM 9107. Univariate analysis identified SIRI scores $\geq 1.9$ as a significant risk factor for OS. Age, sex and high CA 19.9 levels had no prognostic significance for OS in all groups. Patients with EM showed a higher SIRI than those with EM ($p < 0.003$). Patients with SIRI scores $< 1.9$ (55%) compared to those with SIRI scores $\geq 1.9$ (45%) had a longer OS ($p = 0.01$). LM were significantly associated with shorter OS (hazard ratio [HR] $2.99; 95\%$ confidence interval [CI] $1.36-5.34; p = 0.002$) but not those with EM (HR $1.83; CI 0.71-4.72; p = 0.2$). An SIRI $> 1.9$ resulted in a shorter OS compared to an SIRI $< 1.9$ (HR $2.13; CI 1.10–4.10; p = 0.024$).

Conclusions: SIRI is associated with survival in patients with metastatic PC. In patients with LM, unfavourable SIRI may be associated with higher tumour burden. In our experience, a baseline SIRI $> 1.9$ replicates the risk of mortality and this finding may allow better risk stratification.

Legal entity responsible for the study: Medical Oncology Department, Hospital Universitario de La Princesa

Funding: None

Disclosure: All authors have declared no conflicts of interest.
**Antihero-2 therapy efficacy in HER2-negative metastatic breast cancer with HER2-amplified circulating tumor cells: results of the CirCe T-DM1 trial**


**Background**: Changes of HER2 status has been reported in circulating tumor cells (CTC) isolated from preclinical models and metastatic breast cancer (MBC) patients. The prospective multicentric phase II “CirCe T-DM1” trial was set up to assess whether HER2-amplified CTC are detectable in HER2-negative MBC and whether these cancers would respond to anti-HER2 therapy.

**Methods**: HER2-amplified CTC were screened in HER2-negative (HER2-ER/ and HER2-ER+/HER2-E+) MBC patients starting a 3rd line or 4th line of systemic therapy. CTC were detected by CellSearch® (Janssen Diagnostics) and Fish was performed on isolated CTCs. HER2-amplification was defined by a HER2/CEP17 ratio ≥ 2.2. Patients with ≥1 HER2-amplified CTC, measurable disease and adequate organ function were eligible. After stratification according to ameliorated CTC count (< vs > 3 patients), patients received single agent T-DM1. The primary endpoint of the study was the response rate by RECIST.1.1 at 2 months (m) (p = 0.05), progression free survival (PFS) (HR = 0.24 (0.07-0.86), p = 0.05), 6-m PFS (43.8% vs 95%) and overall survival (OS) (HR 0.08 (0.01-0.63), p = 0.02). In all pts with DCB, PFS was found to be 5.6 vs 4.2 m [HR 0.30 (0.14-0.65)], OS was 10 m for 30% and 9 m for 60% (p = 0.007). KEF drop correlated with CD31 reduction in tissue biopsies (p = 0.04). RAS mutant clones decay in ctDNA after 8 weeks of treatment was associated with better PFS (HR 0.23 (0.07-0.71), p = 0.01) and OS [HR 0.28 (0.09-0.74), p = 0.06]. PDCs xenotransplants treated with REG compared to control had significantly lower tumour BV (4.5 VS 10.6, p = 0.03) and lower microvascular density measured by CD31 staining (4.3 VS 8.9, p = 0.02).

**Conclusions**: Combining DCE-MRI and cfDNA predicts depth and duration of antiangiogenic response to REG with potential health economic implications.

**Clinical trial identification**: clinicaltrials.gov number NCT03010722

**Legal entity responsible for the study**: The Royal Marsden NHS Foundation Trust

**Funding**: Bayer Oncology Group

**Disclosure**: K. Khan: Advisory board for Bayer Oncology Group. D. Cunningham: Research funding from: Roche, Amgen, Celgene, Sanofi, Merck Serono, Novartis, AstraZeneca, Bayer, Merrimack and MedImmune. I. Chaur: Advisory roles with Merck Serono, Roche, Sanofi Oncology, Bristol-Myers Squibb, Eli-Lilly, Novartis, Gilead Sciences, Inc., P. Cottu: C21 Oncology, deCODE Genetics, Inc., Colorado Oncology, Inc.; Received consulting fees from: Roche, Sanofi, National Cancer Institute.

**Abstracts**

**118P**

Nationalwide external quality assessment (EQA) of EGFR testing in circulating tumor DNA: The French experience

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**Background**: Detection of EGFR mutation in circulating tumor DNA (ctDNA), a powerful blood-based biomarker with multiple clinical applications for lung cancer patient, is technically challenging because it requires sensitivity and specificity. In order to evaluate the performance of the French laboratories performing this assay, we set up a nationwide EQA scheme for circulating tumor DNA.

**Methods**: Artificial samples were prepared by spiking DNA extracted from control FFPE sections containing specific mutations (Horizon Diagnostics, from 25 to 350 copies/mL of plasma, as determined by digital PCR) in normal plasma (Clinsciences).

Aliquots (2 ml) of 10 different samples were sent in dry ice to 43 laboratories. DNA extraction and EGFR testing were performed according to local practice. Laboratories were requested to search for exon 19 deletions, p.L858R, p.G719X and p.T790M mutations. Results were collected on a web questionnaire within one month and compared to the expected results.

**Results**: We collected 30 complete sets of data. DNA was extracted using the QI Amp® circulating DNA kit (Qiagen, n = 13), the Cobas® ctDNA sample preparation kit (Roche, n = 9) or the Maxsor® system (Promega; n = 7). The most widely used methods were the Cobas® EGFR Mutation Test v2 (Roche; n = 10), digital PCR (n = 8) and NGS (n = 6). Among the 10 labs using the Cobas®, 9 obtained the expected genotypes. This number dropped to 3 (out of 6 labs) for NGS, and 2 (out of 8 labs) for dPCR, because of false negative results, false positive results, and not contributive tests.

**Conclusions**: Digital PCR and NGS are known to be highly sensitive techniques. However, the results of this EQA suggest that in routine clinical practice, ctDNA analysis requires technical skill and validated bioinformatics pipeline to reach high sensitivity and specificity. Under the specific conditions of this scheme, the Cobas® method appeared to be the most robust approach. This external control will allow the laboratories to evaluate their practice and improve their process. A similar approach targeting other genes (BRAF, KRAS and NRAS) is being developed, and additional EQA schemes will be set up at the nationwide level. Supported by a grant from AstraZeneca.

**Legal entity responsible for the study**: GenetiQs

**Funding**: AstraZeneca

**Disclosure**: All authors have declared no conflicts of interest.

**8.8 as a pharmacodynamic biomarker for TGF-f2 antisense (trabedersen) therapy: Results of a phase II trial**

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**Background**: In a Phase I/II study of Trabedersen (OT-101), a phosphorothioate antisense specific for human TGF-f2 mRNA, patients with advanced pancreatic cancer (PAC) treated in the 2nd-line and beyond exhibited improved overall survival (OS) when OT-101 was followed with chemotherapy. Here, we examined the association between plasma levels of cytokine/chemokines and OS outcomes to identify potential biomarkers for improved OS.

**Methods**: 37 PAC patients were treated with continuous IV infusion in escalating doses of 2 treatment schedules (7-days-on, 7-days-off and 4-days-on, 10-days-off). Plasma levels of 51 cytokine/chemokines were measured at 8 separate time points over 3 cycles of OT-101 treatment (140 mg/m2/day, 4-days-on, 10-days-off). Standardized maximum levels of individual cytokine/chemokines on Day 2 were subtracted from levels on Day 3 of each cycle of treatment and correlated with log10 transformed OS values. Feedback interactions with PK parameters were also investigated utilizing an ANOVA model.

**Results**: A median OS of 14.5 months and 2.6 months was observed for 2nd-line patients treated with and without subsequent chemotherapy, respectively (p = 0.0009). Increasing difference of IL-8 levels at Day 2 vs Day 5 was positively correlated with OS (R2 = 0.58, P = 0.0066). Stratifying for patients with and without chemo, R2 increased to 0.99 and 0.77 respectively. Similar results were observed for IL-15, with R2 = 0.93 in patients with chemo and R2 = 0.50 in those without. ANOVA models for two PK parameters exhibited significant model fits (F2,8 = 7.89, P = 0.012 for Simulated Vd Mean, F2,8 = 8.18, P = 0.011 for Simulated CL Mean) and the interaction effects resulted in lower p-values for the correlation of OS vs IL-8 levels.

**Conclusions**: Increasing peak levels of IL-8 and IL-15 response on Day 2 of OT-101 treatment correlated with OS in PAC patients. This correlation with OS was evident regardless of subsequent chemotherapy or not indicating spikes in IL-8 in IL-15 as potential biomarkers for OT-101.

**Legal entity responsible for the study**: Oncotelic Inc

**Funding**: Oncotelic Inc

**Disclosure**: L. Hwang, W. Wang, S. Qazi, K. Ng, O. D’cruz, V. Trieu: Employee
Angiogenesis inhibitors are widely used for treatment of metastatic colorectal cancer. Both bevacizumab (through inhibition of VEGF activation) and cetuximab (through inhibition of EGFR-signaling) would be expected to have anti-angiogenic effects in colorectal cancer. The predictive role of AADx in FOLFIRI plus bevacizumab or cetuximab treated in colorectal cancer patients remains unclear.

Methods: Transectional profiling of 501 formalin fixed paraffin embedded pre-treatment samples from the ITT population was performed using the Almac Diagnostics Xcel® array. Patients were classified by the AADx assay as ANGIO ON or OFF based on a predefined score. ORRs were compared using Fisher's exact test. Progression free survival (PFS) and Overall survival (OS) times were compared using Kaplan-Meier estimation and log-rank tests. Hazard ratios (HR) were estimated according to the Cox proportional hazard method.

Results: The AADx assay was successfully applied to 438 out of 501 specimens available from the study population (n = 752). Of those, 315 had a RAS wt tumor and 123 a RAS mutant. The correlation between RAS status and AADx score with respect to ORR, PFS, and OS were complex (Table). The addition of cetuximab to FOLFIRI was significantly superior to the addition of bevacizumab in “ANGIO ON” tumors most likely reflecting the strong link between EGFR-signaling and angiogenesis in colorectal cancer.

Conclusions: Here, we present data demonstrating that it possible to define subgroups of CRC patients within the FOLFIRI trial that respond differently to the addition of cetuximab or bevacizumab.

Clinical trial identification: NCT00439279

Legal entity responsible for the study: Klinikum der Universität München

Funding: ALMAC Inc.


121P Influence of HIF-2alpha deregulation and overexpression of VEGF ligands on the response to aflibercept: Identification of predictive biomarkers

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Background: Angiogenesis inhibitors are widely used for treatment of metastatic colorectal cancer. However, no predictive biomarkers are currently available for patient selection. Besides the tumor-associated endothelial cells, VEGF-signaling inhibitors target CRC cells that express VEGF as well as functional VEGFR1 receptors thereby mediating both paracrine and autocrine VEGF-signaling. The aims of this work is i) to establish the direct influence of aflibercept (Zaltrap®) that inhibits all three VEGF1 ligands (VEGF-A, VEGF-B and PDGF) on CRC cells, ii) to identify tumor phenotypes associated with resistance to aflibercept in vitro and, iii) to extend these findings to human xenograft models.

Methods: A panel of 12 well-characterized CRC cell lines was used to establish the influence of VEGFR1 stimulation (VEGF-A, VEGF-B, PDGF) and inhibition (aflibercept) on VEGF-mediated tumor cell migration. Expression of VEGF ligands and receptors was determined by qRT-PCR and ELISA assays. The in vivo influence of aflibercept was determined in human xenograft models and complemented by IHC and Western blot analysis.

Results: Aflibercept inhibited the migration of most CRC cells under both normoxia and hypoxia including the highly sensitive HCT-116 cells. In contrast, LS174T cells did not respond to either aflibercept or to purified VEGF ligands. These cells expressed high levels of VEGF ligands and HIF2alpha, even under normoxia. Accordingly, aflibercept showed pronounced in vivo activity toward LS174T xenografts with 79% tumor growth inhibition but only 40% tumor growth inhibition toward LS174T tumors, compared to the corresponding vehicle controls. A similar trend was observed for bevacizumab with 41% tumor growth inhibition for HCT-116 and 52% inhibition for LS174T xenografts. IHC analysis of LS174T xenografts confirmed the strong expression of HIF2alpha and VEGF ligands as well as a modest inhibitory effect on the tumor-associated endothelia cells.

Conclusions: We here report that aflibercept has direct antimigratory effects on most CRC cells. Strong expression of HIF-2alpha and VEGF ligands was accompanied by aflibercept resistance in vitro as in vivo.

Legal entity responsible for the study: INSERM U938 and Université Pierre et Marie Curie (UPMC), Sorbonne Universités, Paris, France

Funding: Sanofi-Genzyme

Disclosure: A.K. Larsen: This work was supported in part by Sanofi Genzyme. E. Dochy: Employed by Sanofi-Genzyme. A. de Gramont: This research is in part supported by Sanofi. All other authors have declared no conflicts of interest.

Table: 120P

<table>
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<tr>
<th>RAS wild-type</th>
<th>AADx score</th>
<th>ORR p OR</th>
<th>PFS months p HR</th>
<th>OS months p HR</th>
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</thead>
<tbody>
<tr>
<td>FOLFIRI + Cetuximab</td>
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<td>46.3%</td>
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</tr>
<tr>
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<td>ANGIO OFF</td>
<td>40.0%</td>
<td>10.2</td>
<td>18.5</td>
</tr>
</tbody>
</table>
To test the prognostic effect of cDNA mutational burden, patients were classified as having high or low variant allele fraction (VAF) in cDNA using the median as a cutoff.

**Results:** In 81 patients (92%), at least one mutation was detectable by cDNA sequencing. Concordance with tissue sequencing was 79%. High VAF was associated with shorter PFS and low VAF in both the IPAT + P arm (HR 2.39 [90% CI 1.19–4.79]) and the placebo + P arm (HR 2.68 [90% CI 1.46–5.11]). High VAF was also associated with the presence of >1 metastatic site but not tumour volume per RECIST v1.1. In 22 patients (25%), an activating PIK3CA (n = 16) or AKT1 (n = 6) mutation was detected in cDNA; concordance with tissue sequencing was 100%. PFS improvement with the addition of IPAT to P was more pronounced in patients with detectable PIK3CA/AKT1 mutations (HR 0.15 [90% CI 0.03–0.50]) than in those without a detectable mutation (HR 0.82 [90% CI 0.50–1.31]).

**Conclusions:** These results highlight the potential role of cDNA in evaluating patient prognosis as well as identifying genetic markers associated with improved treatment outcomes. Furthermore, they support the occurrence of PIK3CA and AKT1 mutations as early genetic events present in primary tissue samples that are maintained during metastasis.

**Clinical trial identification:** NCT02162719

**Legal entity responsible for the study:** F Hoffmann-La Roche Ltd.

**Funding:** F Hoffmann-La Roche Ltd.

**Disclosure:** M. Wengchenko: Employee of Genentech, Inc. and holds shares in Roche and Ariad Pharmaceuticals. R. Dent: Honoria for consultancy/advisory boards/ speaker engagements from Pfizer, Roche, Eisai, Merck, and AstraZeneca. S-B. Kim: Research funding from Novartis, Sanofi-Aventis, Kyowa Kirin Inc and Dongkook Pharma Co., Ltd. C. Saura: Honoria for consulting/advisory roles from Puma Biotechnology, Pfizer, and Roche and research funding (to her institution) from Genentech and AstraZeneca. M. Oliveira: Honoria for consulting/advisory roles from Puma Biotechnology and Genentech/Roche and research funding (to the institution) from Genentech and AstraZeneca. J. Basela: Compensation for a leadership role from Puma Biotechnology to EGFR and EGFR domain (ECD), and amplifications in MET/ERBB2. Studies suggest that some anti-EGFR antibodies (mAbs) is frequently due to mutations in RAS/BRAF and EGFR extracellular domain (ECD). Accession of mCRC patients highly sensitive to Sym004 is discussed. Comprehensive liquid biomarker profiling of 193 mCRC pts captured outcomes. Furthermore, they support the occurrence of PIK3CA and AKT1 mutations as early genetic events present in primary tissue samples that are maintained during metastasis.

**Background:** Acquired resistance of mCRC patients (pts) to anti-EGFR monoclonal antibodies (mAbs) is frequently due to mutations in RAS/BRAF and EGFR extracellular domain (ECD), and amplifications in MET/ERBB2. Studies suggest that some anti-EGFR antibodies (mAbs) is frequently due to mutations in RAS/BRAF and EGFR extracellular domain (ECD). Accession of mCRC patients highly sensitive to Sym004 is discussed. Comprehensive liquid biomarker profiling of 193 mCRC pts captured outcomes. Furthermore, they support the occurrence of PIK3CA and AKT1 mutations as early genetic events present in primary tissue samples that are maintained during metastasis.
Results: Of 69 plasma cfDNA samples collected from patients (cancer: 54, non-cancer: 15), DNA mutations were identified in 53 patients in circulating tumor cells. These included 11 patients with CNGs, 5 with single-cell combined mutation and expression studies, 15 with single-cell combined mutation and expression studies of circulating tumor-associated cells in non-small cell lung cancer progression and/or on therapy. Up to 30 ng (median 18 ng) of plasma cfDNA was tested with the pan-cancer methylation panel to target a total of 10,888 CpG sites using an Illumina HiSeq2500 sequencer to calculate methylation scores. Methylation scores were correlated with cancer types and clinical outcomes.

Conclusions: Single-cell combined mutation and expression studies of circulating tumor-associated cells in non-small cell lung cancer may predict TKI sensitivity but when acquired are postulated to reflect resistance. Treatment with monoclonal antibodies may have a role and therefore CNA integration in molecular diagnostics is potentially important.

Funding: Agency for Science, Technology and Research (A*STAR)

Disclosure: All authors have declared no conflicts of interest.

127P EGFR copy number aberrations detected in cfDNA from advanced NSCLC patients

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Background: Copy number aberrations (CNA) in the epidermal growth factor receptor (EGFR) represent a mechanism of tyrosine kinase activation and oncogenic signaling in advanced non-small cell lung cancers (NSCLC). High copy number gains (CNGs) of EGFR may predict TKI sensitivity but when acquired are postulated to reflect resistance. Treatment with monoclonal antibodies may have a role and therefore CNA integration in molecular diagnostics is potentially important.

Methods: Cell free (cf) DNA was extracted from plasma of advanced cancer patients undergoing treatment with EGFR-TKIs. A validated Liquid Biopsy Sequencing (LB-Seq) method for hybrid capture followed by ultra deep sequencing (> 20,000x) evaluated coding exons of KRAS, NRAS, BRAF, PIK3CA, and EGFR (18 kb). Subsequent filtering of mutation calls using a novel algorithm enabled detection of tumor-derived fragments at concentrations down to 0.2%. EGFR CNAs were assessed using a modified version of the VisaCap algorithm. Mutation calls were compared to tissue biopsy results for EGFR mutations.

Results: Targeted sequencing has been performed on 12 samples to date: 10 patients with classical EGFR mutations in L858R and delE746-747, 1 with an exon 20 insertion and 1 with an exon 18 G719X mutation. All patients had progressed on at least one EGFR-TKI. 13 mutant reads ranged from 0.25% to 33%. EGFR CNAs were detected in 3 patients: 1 patient with T790M + ve disease confirmed in both tissue and cfDNA was found to have a co-occurring BRAF mutation (p.334G>A). The remaining 2 patients’ tissue samples tested negative for T790M, T790D was detected in cfDNA in 1 patient, who is currently receiving osimertinib, and in the other patient rapid progression on gefitinib occurred with an EGFR-G719X mutation. Copy number losses were detected in 2 patients. Of 6 patients with EGFR-T790M positive tissue were verified by ddPCR. An intronic variant of unknown significance (c.747 + 9C>T), not covered in tissue testing, was also captured in cfDNA.

Conclusions: Copy number aberrations in EGFR can be detected from targeted sequencing of cfDNA in patients with EGFR mutated NSCLC. Longitudinal evaluation in patients receiving EGFR-TKIs may provide insights into mechanisms of resistance.

Legal entity responsible for the study: Natasha Leigh

Funding: None

Disclosure: N.B. Leigh. Research funding (institution): Novartis. Travel/honoraria: AstraZeneca, Merck Sharp Dohme, Pfizer, Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

128P Detection of esophageal cancer patients using circulating serum microRNA from the result of comprehensive analysis

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Background: Recent studies have reported that serum microRNAs (miRNAs) are potentially useful biomarkers for diagnosis and treatment of cancer. However, its utility for detecting esophageal squamous cell carcinoma (ESCC) has not been investigated yet. The aims of this study are to identify circulating serum miRNAs for ESCC detection.

Methods: We comprehensively analyzed serum miRNA expression profiles of 595 patients with ESCC, and 5051 non-cancer individuals using microarray (3D-Gene, Toray). Serum of non-cancer individuals was obtained from Biobank of NCGG and Health check up clinic (Yokohama Minoru clinic). Serum of ESCC patients was collected before starting any treatment such as radiotherapy, surgery and chemotherapy. Analyzed samples were randomly divided into discovery and validation sets. Serum miRNA levels were compared between ESCC and non-ESCC patients. Fisher’s linear discriminant analysis was performed to construct the discriminant model for ESCC detection. Measured values of each miRNA were extrapolated into the discriminant formulas. We performed ROC analysis to evaluate the diagnostic ability of these formulas in each validation cohort.
Results: In discovery set, 300 patients of ESCC was compared to 300 individuals of non-cancer control. We picked up 3 miRNAs, named miR-a, miR-b and miR-c, for ESCC, diagnosis. Their AUC for detection of ESCC was 0.967, 0.873 and 0.650, respectively, and HR was 4.28, 3.70 and 1.82, respectively. We constructed the discriminant model, called EC index, using these 3 miRNAs in discovery set. In validation set which contain 295 pts of ESCC and 4751 person of non-cancer control, EC index showed the AUC, sensitivity and specificity of the discriminant formula was 0.99, 0.98 and 0.95, respectively.

Conclusions: We identified novel serum miRNAs for ESCC detection. Our discriminant using these miRNAs can diagnose ESCC.

Clinical trial identification: NC0092016-249

Legal entity responsible for the study: National Cancer Research and Development

Funding: Japan Agency for Medical Research and Development


First prospective multicenter real-world RAS mutation comparison between OncoBEAM-based liquid biopsy and tissue analysis

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Background: Liquid biopsy is a powerful tool to refine the management of cancer patients by offering a minimally-invasive alternative to tumor tissue testing and rapid evaluation of overall tumor burden mutational status. To support its clinical adoption, a rigorous real-world evaluation of this method in routine clinical practice is required.

OncoBEAM RAS is the only liquid biopsy assay to attain CE-IVD status for plasma RAS mutational analysis in routine colorectal cancer (CRC) patient care. The goal of the present study was to evaluate the aggregate performance of OncoBEAM RAS in 10 hospital labs where the technology is installed in Spain.

Methods: Blood samples were collected in Streck cell-free DNA BCT® or EDTA tubes from metastatic CRC patients and circulating cell-free DNA from plasma was examined for RAS mutations using the OncoBEAM platform at each hospital laboratory. Results were then compared to those obtained from DNA extracted from tissue from the same patient.

Results: The overall percentage agreement (coincidence) of results from plasma and tissue RAS mutation testing of 230 patients was 90.4% (208/230); 95% CI = 0.86-0.94, with positive percent agreement of 86.9% (131/150) and negative percent agreement of 99.5% (108/110). We performed a blinded clinical follow-up analysis of 95 patients who had detectable RAS mutations in plasma. Out of 95 patients, 93 (97.9%) had progression under TKI while 2 (2.1%) remained stable.

Conclusions: In this first prospective real-world RAS mutation performance comparison study across a network of hospital laboratories certified to perform OncoBEAM testing in routine clinical practice, a high overall agreement was observed between results obtained from plasma and tissue samples. These results are comparable to those obtained in retrospective studies. Overall, these findings indicate that plasma OncoBEAM RAS testing is a viable solution for rapid delivery of RAS mutation status to determine mCRC patient eligibility for anti-EGFR therapy.

Legal entity responsible for the study: University Hospital “Fundacion Jimenez Diaz”, Autonomous University of Madrid

Funding: Symyx, Merck

Disclosure: All authors have declared no conflicts of interest.

EGFR plasma testing in routine practice by real-time PCR in lung cancer patients: Experience of 262 patients

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Background: EGFR mutation testing in lung cancer prior to tyrosine kinase inhibitor (TKI) therapy can be performed in tissue or plasma in practice. Both techniques are complementary; however, plasma testing can represent a surrogate for re-sampling a tumour in patients progressing under TKI prior to prescription of osimertinib, but clinical sensitivity of the test remains to be determined. We present our twelve-month experience of integrating EGFR plasma testing into our service with a series of 262 cases.

We currently receive over 50 cases per month.

Methods: EGFR mutation testing for both tissue and plasma is performed using cobas EGFR Mutation Test v2, which covers 29 deletions in exon 19, T790M, L858R, G719X, S768I, L861Q and 5 insertions in exon 20. Plasma testing. DNA is extracted using the cobs cDNA sample preparation kit. All samples were submitted in Paxgene cDNA tubes.

Results: Of the 262 cases submitted for testing, five failed (1.9%): 123 mutations, including 42 T790M, were detected. Turnaround time was two days. Clinical sensitivity is very difficult to assess because of the uncertainty of the presence of circulating tumour DNA at all. All types of primary mutation were detected: 70 exon 19 deletions, 42 L858R, 2 G719X, 5 S768I, 3 combined S768I and G719X, and 1 singlet T790M.

Clinical details were not available for all patients. A sensitising mutation was found in 51 of 92 patients (55.5%) under TKI therapy, where this was indicated on the request form; among these, an associated T790M mutation was found in 19 (35%) of patients. Several patients underwent multiple tests while they received TKI therapy; in two patients, the secondary mutation was detected prior to clinical progression.

Conclusions: We show here that EGFR plasma testing is perfectly suitable for clinical practice; it is highly specific and cost-effective due to rapid turnaround times, but the low sensitivity renders it complementary to tissue testing rather than a true surrogate.

Legal entity responsible for the study: N/A

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Circulating tumor cells as liquid biopsy for castration resistant prostate cancer patients treated with cabazitaxel

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Background: Cabazitaxel (CBZ) has been shown to improve overall survival (OS) in metastatic castration resistant prostate cancer (mCRPC) patients (PSA ≥10). However, clinical benefit is variable and progression-free survival (PFS) is limited. CBZ treatment failure is often due to the development of resistance to docetaxel (DOC). Circulating tumor cells (CTCs) expression profiling before CBZ treatment could establish novel predictive biomarkers.

Methods: We prospectively enrolled 28 pts with mCRPC treated with CBZ 25 mg/m² after DOC and abiraterone or enzalutamide. CTCs enrichment was assessed with Adna Test EMT/STEM. Expression analyses of AKR1C3, AKT2, ALDH1, AR, ARV7, EPCAM, FOLH1, HPRT1 were analyzed using real time PCR. CTCs positive pts were defined when at least one marker among AKT2, AR, AR-V7, EPCAM, FOLH1, HPRT1, PSCA, PIK3CA were expressed. Progressive disease was defined according to PCWG2 criteria. Main endpoint was the correlation between CTCs expression profiling and outcome.

Results: Of these 28 pts, 18 (64%) had detectable CTCs before the starting of CBZ and 10 (36%) had undetectable CTCs. Detection of CTCs was associated with poor OS. However, no difference was observed for progression-free survival (PFS). No correlation between CTCs assessment and PSA response rate was found. In addition, we subdivided pts according to median value of CTCs expression markers. Nine (50%) pts with ≥3 markers had a significant worse PSA compared to pts with <3 markers. Pts with ≥3 markers, reflecting heterogeneous of disease, had also a poor OS (Table).

Table: 131P

<table>
<thead>
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<th>CTCS</th>
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<th>PFS</th>
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<td></td>
<td>Median (months)</td>
<td>HR (95% CI)</td>
<td>p</td>
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<td>18/28 5.8</td>
<td>1.31 (0.18-8.50)</td>
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<td>≤3 markers</td>
<td>9/18 2.5</td>
<td>3.59 (0.07-7.0)</td>
<td>p=0.0039</td>
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<td>≥3 markers</td>
<td>9/18 10.1</td>
<td>12.01 (0.4-21.03)</td>
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</table>

Conclusions: We prospectively confirmed a prognostic role for CTCs in mCRPC pts treated with CBZ and we also firstly showed the utility to characterize CTC expression markers thanks to its potential predictive role. The identification of markers expressed
Biomarker analysis using circulating tumor DNA in patients treated with sorafenib for advanced hepatocellular carcinoma

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Background: We aimed to investigate potential biomarkers in patients treated with sorafenib for advanced hepatocellular carcinoma (HCC) using circulating tumour DNA (ctDNA).

Methods: 155 patients who had started sorafenib between March 2014 and November 2016 were identified from a prospective biomarker cohort of Asan Medical Center, Korea. We quantified the concentration of ctDNA extracted from blood samples of each patient collected before sorafenib treatment and measured the copy numbers of vascular endothelial growth factor-A (VEGFA) in ctDNA. We also applied low depth whole genome sequencing from ctDNA to find copy number aberrations in HCC and employed Q-score, defined as a standard deviation regarding Z-scores of sequenced reads on each chromosome.

Results: Among 155 patients, 124 were finally included in the analysis. 82 patients achieved partial response, stable disease or non-CR/non-PD with sorafenib treatment (non-PD group) whereas 42 exhibited progressive disease (PD group). The PD group did not differ between PD (n = 16) and non-PD (n = 25) groups (2.56 vs. 2.48; p = 0.467). Divided into two groups based on the median value (119.7 ng/mL) of ctDNA concentrations, patients with high ctDNA had significantly shorter time to progression (TTP) (median, 2.3 vs. 4.1 months; p = 0.038). Q-score of PD group was also higher than that of non-PD group but there was a borderline significant difference between two groups (6.10 vs. 5.80; p = 0.056). VEGFA copy number, which was available for only 41 patients, did not differ between PD (n = 16) and non-PD (n = 25) groups (2.56 vs. 2.48; p = 0.467). Overall survival (OS) (median, 4.5 vs. 14.8 months; p < 0.001) was lower for those with low ctDNA. Similarly, patients with higher Q-score than median value of 4.12 had significantly worse TTP (median, 2.7 vs. 4.0 months; p = 0.012) and OS (median, 5.2 vs. 17.3 months; p < 0.001) compared to those with lower Q-score. After adjusting confounding factors by multivariate Cox regression analysis, the concentration of ctDNA and Q-score remained independent prognostic factors associated with both TTP (p = 0.026 and 0.042, respectively) and OS (p = 0.001 and p = 0.001, respectively).

Conclusions: Our results showed that ctDNA level and copy number aberrations represented by Q-score could be potential prognostic biomarkers in HCC patients treated with sorafenib.

Legal entity responsible for the study: Department of Oncology, Asan Medical Center, Seoul, Republic of Korea

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Background: Currently, pathological staging according to the tumor-node-metastasis system remains the gold standard for the prediction of patient survival in colorectal cancer (CRC) but this classification system provides insufficient information and therefore additional prognostic markers are needed.

Methods: A genome-wide methylation analysis was done for two independent cohorts of non-metastatic CRC patients (screening cohort n = 578 and validation cohort n = 308). Initially, genome-wide differentially methylated CpG sites between 34 pairs of tumor and normal mucosa tissue samples from the same patients were identified. A variable screening for prognostic CpG sites was performed in the screening cohort using marginal likelihood based on the Cox model and subsequent adjustment of the p-values via independent hypothesis weighting (IHW) using the difference between tumor and normal mucosa tissue as auxiliary covariate. From the 1000 CpG sites with the smallest adjusted p-value, the 20 CpG sites with the smallest Brier Score for 3-year overall survival (in the screening cohort) were selected. Applying principal component analysis on these CpG sites, we derived a methylation-based classifier for the prognosis of non-metastatic CRC (ProMcO).

Results: The ProMcO classifier was independently validated in the validation cohort, where it showed a significant reduction in the Brier score. Regarding the three year survival, the prediction error was reduced from 0.132 (calculated only with clinical variables), to 0.124 (combination of clinical variables with ProMcO classifier).

An additional replication analysis showed that the ProMcO classifier was significantly associated with overall survival (OS) of non-metastatic CRC patients in the screening (HR = 0.42, 95%CI 0.33-0.55, p=0.005) and the validation cohort (HR = 0.40, 95%CI 0.22-0.74, p=0.003), adjusted for standard clinical factors. Patients with a high methylation status, represented by higher values of the ProMcO classifier, showed a better prognosis for OS than patients with a low methylation status and lower ProMcO classifier values.

Conclusions: The usage of the ProMcO classifier could improve the prognostic accuracy for non-metastatic CRC patients.

Legal entity responsible for the study: Barbara Burwinkel, German Cancer Research Center

Funding: German Research Council, German Federal Ministry of Education and Research

Disclosure: All authors have declared no conflicts of interest.
Results: Hundred fifty-three samples (17.6%) were classified as MSI-H and 693 samples (79.7%) as MSS with the novel set of biomarkers, while 24 samples (2.8%) could not be classified. Concordance analysis was performed on 201 samples. The overall percent agreement with results available for both methods (137/201) was 93.6%. 11/173 (6.4%) were scored MSI-H for Idylla and MSS for the reference method; conversely no MSI-H cases for the reference method and MSS for Idylla were detected. 24/201 (11.9%) samples failed with the reference method, even after repeat testing, while only 26/201 (4.0%) samples failed with the Idylla methodology.

Conclusions: This study on a diverse set of CRC samples successfully demonstrated the validity of the novel MSI biomarkers to discriminate between MSI-H and MSS status. The Idylla MSI Test is currently under development on the most performant markers. Compatibility with the fully integrated Idylla platform will allow providing accurate and reliable results, with actionable results generated within 150 minutes from just one tumor FFPE slice (no reference sample required).

Legal entity responsible for the study: Biocartis NV

Funding: None


139P Gene expression BIRC5, Erb-b2/Her2-neu, ESR1, PGR1, MMP11, MDR1, MRP1, MXR at the CTCs in the primary breast cancer

Y. Shakhtronsky
Oncology, Vitebsk State Medical University, Vitebsk, Belarus

Background: Distant metastases are the main cause of death of patients with breast cancer. The substrate for the development of metastases are the circulating tumor cells (CTCs). Determination of the expression of tumor-specific genes gives a more complete picture of the course of the tumor process.

Methods: Using PCR technology in real-time, gene expression studied BIRC5, Erb-b2/Her2-neu, ESR1, PGR1, MMP11, MDR1, MRP1, MXR at the CTCs in the surgical and adjuvant treatment of 56 cases primary non-metastatic breast cancer.

Results: In 33 (59%) prior to surgery functionally active in the CTCs-enriched periph-

Table: 140P Univariate analyses of progression-free survival (PFS) and overall survival (OS) according to Metabolic Syndrome (MS) and Inflammation (INF) status

<table>
<thead>
<tr>
<th></th>
<th>Median PFS (months) (95% CI)</th>
<th>HR (95% CI) p</th>
<th>Median OS (months) (95% CI)</th>
<th>HR (95% CI) p</th>
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</thead>
<tbody>
<tr>
<td>Overall</td>
<td>7.4 (6.4-7.8)</td>
<td></td>
<td>17.6 (15.5-19.0)</td>
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</tr>
<tr>
<td>Baseline MS</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>8.3 (7.4-9.2)</td>
<td>&lt;0.0001</td>
<td>1.00 (1.3-1.7)</td>
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</tr>
<tr>
<td>Yes</td>
<td>3.7 (5.5-4.1)</td>
<td>&lt;0.0001</td>
<td>2.77 (2.12-3.61)</td>
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<td>Baseline INF</td>
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<tr>
<td>No</td>
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<td>&lt;0.0001</td>
<td>1.00 (1.3-1.7)</td>
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<tr>
<td>Yes</td>
<td>4.5 (3.7-5.9)</td>
<td>0.002</td>
<td>1.48 (1.15-1.90)</td>
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<tr>
<td>Combination MS+INF</td>
<td>9.0 (7.6-9.2)</td>
<td></td>
<td>1.00 (1.3-1.7)</td>
<td></td>
</tr>
<tr>
<td>MS- &amp; INF+ 1</td>
<td>1.00 (1.3-1.7)</td>
<td>&lt;0.0001</td>
<td>130/218 (20.4 (16.5-24.0)</td>
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<tr>
<td>MS- &amp; INF+ 2</td>
<td>1.25 (0.9-1.68)</td>
<td>0.002</td>
<td>46/85 (18.0 (11.1-22.4)</td>
<td>1.25 (0.89-1.76)</td>
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<tr>
<td>MS+ &amp; INF+ 3</td>
<td>3.7 (2.0-6.84)</td>
<td>&lt;0.0001</td>
<td>73/11 (6.5 (3.0-11.2)</td>
<td>3.80 (2.04-7.09)</td>
</tr>
</tbody>
</table>
141P Ischemic stroke and cancer recurrence: A stroke unit experience

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Background: Cancer (Cr) and ischemic stroke (IS) are common causes of death in high-income regions. Cr patients present a higher probability of developing thromboembolic events, particularly IS. Measurable objective parameters may be helpful stating a neoplastic etiology: High D-dimer (DD) levels; C-reactive protein (CRP); Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) express the severity of inflammation relating it to etiology and prognosis. Single centre retrospective studies usually analyses patients with IS and active solid Cr (NOC) with purpose of identifying clinical, laboratory and imagiological features that differentiate this from a control group (CG) without Cr.

Methods: Patients with IS admitted in a Stroke Unit from 01/2009 to 12/2014. Active cancer identified in clinical process. Transient ischemia, haemorrhagic strokes and other diagnosis excluded. For CG an age and gender matching patient was chosen. Clinical, analytical and imagiological features were compared between groups.

Statistical analysis using the SNPS Statistica V22.

Results: Out of 603 consecutive patients with IS, 48 (7.9%) had active solid Cr, 16 diagnosed during diagnostic work-up for IS, 24 before and 8 in the year after. Male predominance: 30 (62,5%) vs 18 (37,5%) in NOC. Most frequent Cr diagnosed were prostate and bladder (12,5% each); colon (10%) and lung (8,3%). Cardioboombolism was the main subgroup in both (26 NG; 24 CG). Imagiological pattern was similar in both groups. NOC had increased laboratory values compared to CG: LDH 662 vs 501 U/L (p 0,04); CEA 5,2 vs 1,8 mg/dl (p 0,11) and D-D 0,85 vs 0,74mg/ml (p 0,28). Average NLR and PLR: 5,4 and 161,6 NG vs 2,34 and 104,1 CG (p < 0,01 and 0,03 respectively). NG and CG average NIHSS was 63 vs 4,9 (p 0,18) and mRs was 2,75 vs 1,95 (p 0,019) respectively. Higher NLR and PLR were associated with worse outcomes (higher NIHSS and mRs score).

Conclusions: Although Cr is a rare cause of stroke, it should not be devalued. There are several clinical, laboratory and imagiological signs of underlying neoplastic disease that should be considered, since they may promote an earlier diagnosis and approach to this pathology. Future prospective studies should be started in order to validate some of this parameters as indicators of subjacent neoplastic disease.

Legal entity responsible for the study: Mariana Rodrigues

Funding: None

Disclosure: All authors have declared no conflicts of interest.

143P A comparison of treatment recommendations by molecular tumor boards worldwide

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Background: Precision oncology holds promise to improve patient outcome. Yet, a benefit of personalized therapy in comparison to standard therapy has not been shown in prospective trials. We asked molecular tumor boards (MTB) worldwide to make treatment recommendations for sample patients to assess standards and differences in the precision oncology approach.

Methods: 4 fictional patients with various degrees of genomic information (mutation, gene expression, copy number and gene fusion data, somatic and germline events) were created. A questionnaire was designed to identify methods and structures of the respective molecular tumor board’s recommendation process. 29 molecular tumor boards from 9 countries were identified and asked to participate in the survey between August 2016 and March 2017. A qualitative interpretation of the results was performed.

Results: 5 MTBs from 4 countries completed the questionnaire and provided therapy recommendations. An identical treatment recommendation by all 5 MTB was not made for any one of the patients. In only one patient an overlapping treatment recommendation was made by three MTBs. Heterogeneity was larger for patients with more complex genomic information. The availability of clinical trials did not influence the recommendation heterogeneity. The setup of MTBs showed similarities in participating specialists (e.g. medical oncology, pathology, molecular biology), duration of discussion, testing methods and number of discussed patients. Differences were seen in the interpretation process. Further differences were identified in the interpretation of germline aberrations and interpretation of variant allele frequency. Comments by MTBs helped to identify minimum reporting standards for genetic testing.

Conclusions: Several differences in treatment recommendations were observed. In cases with obvious recommendations there was higher concordance among assessments. However, differences in treatment recommendations were observed in complex cases, and such heterogeneity contributes to the complexity of precision oncology. Larger studies are necessary for rational and stepwise development of principles and practice of MTB procedures.

Legal entity responsible for the study: Damian Rieke

Funding: None

Disclosure: U. Keilholz: Speaker honoraria and advisory board roles are with AstaRezena, Bristol-Myers Squibb, Merck, MSD, Pfizer, Novartis, Innate. Corporate-sponsored research with AstraZeneca and Merck. All other authors have declared no conflicts of interest.

144P Identification of germline mutation using 30-gene sequencing and clinical characteristic of Chinese with hereditary breast cancer

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Background: With the recent discovery of other breast cancer susceptibility genes (e.g. CDH1, ATM, CHEK2, PALB2, RAD51), molecular diagnosis of hereditary breast and ovarian cancers (HBOC) using multigene panels could help to identify other moderate/low penetrance genes in patients who tested negative for BRCA1 mutation. However, the clinical management of these cancer predisposition genes have not been clearly defined, therefore only BRCA1 and BRCA2 are routinely included in the genetic screening. In view of the differences in the mutation spectrum across ethnicity, it is important to identify other HBOC genes to estimate the associated breast cancer risk in Chinese.

Methods: High-risk breast cancer patients who were negative for BRCA1, BRCA2, TP53 and PTEN were selected from the Hong Kong Hereditary Breast Cancer Family...
Registry between 2007-2016. In the study, 745 patients were subjected to 30-gene panel by next-generation sequencing (Color Genomics). All detected pathogenic mutations were further validated by bi-directional DNA sequencing. The sequencing data was analyzed by our in-house developed bioinformatics pipeline.

**Results:** Thirty-five pathogenic variants were identified in this series (4.7%), which correspond to 11 different cancer predisposition genes. Majority of the carriers (74.29%) had early-onset of breast cancer (age <45), 42.86% had 2 family members with cancer and 17.14% were triple-negative. The most common mutated genes were PALB2 (12.1%), RAD51D (0.94%) and ATM (0.67%). However, the cancer risk of RAD51D in breast cancers warrants further investigation. Moreover, over 28% of patients had a variant of unknown significance (VUS) in these genes (excluding BRCA1, BRCA2, TP53 and PTEN), which are cost-effective and can help to understand the genetic risk and aid the development of effective treatments.

**Legal entity responsible for the study:** Ava Kwong

**Funding:** None

**Disclosure:** All authors have declared no conflicts of interest.

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**145P Selecting patients with metastatic colorectal cancer for treatment with temozolomide by using proteomic analysis of MGMT**


**Disclosure:** This study was funded by NantOmics, LLC. The collection of FFPE tissue samples used in this study was funded by NantOmics, LLC. NantOmics is an employee held company of NantKwest. All authors have declared no conflicts of interest.

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**Background:** Temozolomide (TMZ) is a standard treatment for melanoma and glioblastoma and it has shown limited but encouraging activity in patients with metastatic colorectal cancer (mCRC). In multiple cancer types, the DNA repair protein O6-methylguanine-DNA methyltransferase (MGMT) is a resistance marker for TMZ. MGMT promoter methylation is associated with loss of MGMT expression and response to TMZ. We hypothesized that mCRC patients whose tumors expressed quantities of MGMT protein below a pre-defined cutoff would have better outcomes on TMZ than patients with MGMT expression above the cutoff. To test our hypothesis, we assessed MGMT by mass spectrometry in the tumor samples of patients with refractory mCRC and MGMT promoter methylation receiving TMZ.

**Methods:** Archived formalin-fixed, paraffin-embedded tissue sections were obtained from 24 patients from two phase 2 trials. A pathologist marked the tumor areas, which were microdissected and solubilized. In each tumor sample, multiple protein biomarkers including MGMT were quantified with selected reaction monitoring mass spectrometry. An MGMT cutoff of 200 amol/mg was based on the limit of quantitation from a concentration curve. The Mantel-Cox log-rank and the Fisher’s exact tests were used for survival comparisons.

**Results:** MGMT protein was detected in 13 of 24 (54.2%) colorectal tumor samples (range: 229.3-784.8 amol/mg). The overall response rate was 29%. Patients with MGMT protein levels below a cutoff of 200 amol/mg (n = 11) had a notably higher response rate than patients with MGMT levels above the cutoff (46% vs. 9%; p = 0.013, Fisher’s test). Also a longer observed (4.5 vs. 1.6 months, HR = 0.36, 95% CI = 0.13-1.10, p = 0.054). Results for overall survival were consistent but not statistically significant (8.9 vs 6.9 months, HR = 0.55, p = 0.221).

Conclusions: Patients with mCRC whose tumors expressed low or undetectable levels of MGMT protein had better outcomes following TMZ treatment than their counterparts. Quantitative proteomic analysis of MGMT could potentially be used to select CRC patients for TMZ treatment. The results of validation studies are forthcoming.

**Legal entity responsible for the study:** NantOmics

**Funding:** NantOmics

**Disclosure:** S. Schwartz, F. Cecchi, Y. Tian, K. Scott, T. Hembrough: Employee at NantOmics. All other authors have declared no conflicts of interest.

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**146P Predicting response to chemotherapy in gastric cancer patients randomized to docetaxel: A reevaluation of the ITACA-S trial**


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**Background:** We have conducted the Nationwide Cancer Genome Screening Project in Japan since April 2015 using Next Generation Sequencing in cancers of digestive system, called as the SCRAM-Japan GI SCREEN. In this presentation, we show the results of advanced pancreatic cancer (aPC).

**Methods:** This study is ongoing with the participation of 20 major cancer centers. Patients who plan to or receive systemic chemotherapy were eligible. DNA and RNA were extracted from FFPE tumor samples and were analyzed by the Oncomine Cancer Research Panel (OCR) which allows to detect homozygous deletion of Copy Number Variant (CNV) and fusions across 143 genes in a CLIA certified CAP accredited laboratory. The detected genomic variant data were classified according to genetic drivers of cancer including gain- and loss-of-function or single nucleotide variant based on the Oncomine Knowledgebase. In this presentation, we show the results of aPC cohort.

**Results:** As of 31st October 2016, a total of 179 aPC samples were analyzed. The sequence with the OCR was successfully performed in 120 (67.0%). Out of 120 patients, the proportion of location of tumor site and histology is as follows: PS-44%, PDAC-97%. The proportion of procedure for sample collection is follows; surgical section 35.0%, needle biopsy 38.3%, EUS-FNA 20.0%, other 5.8% and unknown 0.8%. The frequently detected mutations (> 10%) in 120 samples of which results were available were KRAS (93%), TP53 (63%), CDKN2A (12%), and SMAD4 (11%). Other
important/druggable mutations were GNAS, BRCA2, and ATM (3%, each). Most frequently detected CNVs (≥7 copies) was MYC (3%), and no gene fusion was detected.

Conclusions: This nationwide screening system is efficient to detect rare gene alterations in aPC. Alterations in potentially druggable genes were limited in aPC, but homologous recombination repair genes were attractive target. This novel knowledge provides an intriguing background to investigate new target approaches and represents a progress toward more precision medicine.

Clinical trial identification: Clinical trial information: UMIN000016344

Legal entity responsible for the study: SCRUM-Japan GI-SCREEN

Funding: 13 SCRUM-Japan collaborating pharmaceutical companies, AMED, NCC

Background: F is a selective estrogen receptor degrader for HR + advanced breast cancer patients (pts). We designed this trial to compare A, in combination with F (A+F) to address the hypothesis that a complete estrogen blockade can prevent resistance to aromatase inhibitors in the adjuvant setting.

Methods: This was a multicenter, open label, phase III study in which HR + /HER2- postmenopausal pts were randomized 1:1 to A for 5 years (y) or A+F (A concurrent with F 250mg/4 weeks for 3 y followed by 2 y of F). Pts were stratified for prior chemotherapy (yes/no); number of positive lymph-nodes (0/1-3/4); HR status (both HR+ and HR–); and site. Primary objective was disease-free survival (DFS). Secondary endpoints were disease recurrences and survival from medical records for a further 3 y. The preplanned protocol-specified subgroup analysis suggested greater benefit in HR+ pts. Overall survival data are not yet mature.

Results: From January 2008 to June 2010, 457 pts were randomized to A and 435 to A+F. Pts characteristics were well balanced between arms; median age was 62 y (40–86); 46.9% were N0, 90.5% ER+/PR+ and 68.2% had received prior chemotherapy. Treatment was completed as planned by 72.5% and 48.3% of A and A+F pts. Median relative dose intensity was 99% for A (both arms) and 81% for F. Most relevant G2-3 toxicities (>3% in either arm) with A vs. A+F were hypertension (13.2%; 9.9%), fatigue (5.2%; 11.8%), LDL-Cholesterol increase (9.4%; 5.3%), osteoporosis (5.3%; 6.9%) and musculoskeletal bone/joint pain (26.3%; 29.4%). After a median follow-up of 6.9y, the proportion of pts disease free at 5 y was 90.9% (A 90.77%; A+F 91.25%; D = 0.48%, p = 0.357); 9.4% had BC relapse (A 10.5%; A+F 8.3%; D = 2.2%) and 4.3% had secondary tumors (A 3.9%; A+F 4.4%). Survival and breast cancer-specific survival were not reached.

Conclusions: The GEICAM/2006-10 study failed to demonstrate a statistically significant increase in DFS adding F to A as adjuvant therapy, though no formal conclusion can be extracted from this trial due to the F administered dose and the actual trial sample size.

Clinical trial identification: NCT00543127

Legal entity responsible for the study: GEICAM Spanish Breast Cancer Group

Funding: AstraZeneca AstraZeneca AstraZeneca AstraZeneca

Disclosure: M. Martin Jimenez: Speaker honoraria and AstraZeneca advisory boards participation. J.M. Baena-Canada: Consulting/relationship advice for AstraZeneca. M. Muñoz: Advisory Board from AstraZeneca. All other authors have declared no conflicts of interest.
Efficacy and safety of biosimilar ABP 980 compared with trastuzumab in HER2 positive early breast cancer

G. von Minckwitz1, O. Ponomarenko2, S. Morel3, N. Zhang4, V. Hanes5

1Medicine and Research, German Breast Group (GBG) Forschungs GmbH, Neu-Isenburg, and stockholder of Amgen Inc. All other authors have declared no conflicts of interest.

Background: Analytical, functional, and pharmacokinetic similarity between ABP 980 and trastuzumab (TRAS) has been demonstrated. Here we report the results of primary efficacy analysis in the corresponding clinical study.

Methods: The objective of this randomized, multicenter, double-blind study was to compare ABP 980 with TRAS on pathologic complete response (pCR) in women with HER2 positive early breast cancer. After run-in anthracycline-based chemotherapy, patients were randomized 1:1 to intravenous ABP 980 or TRAS plus paclitaxel Q3W for 4 cycles. Patients had to complete a full cycle of run-in therapy to be eligible for randomization. Patients continued to the adjuvant phase on IP Q3W for up to 1 year. The co-primary endpoints were risk difference (RD) and risk ratio (RR) of pCR in breast tissue and axillary lymph nodes of tumor samples. Clinical similarity was confirmed if the 2-sided 90% CIs for RD and RR were within the bioequivalence margin of -13% to 13% for RD and 0.79 to 1.38 for RR. Secondary endpoints included safety.

Results: Of the 827 enrolled patients, 725 were randomized (ABP 980: n = 364; TRAS: n = 361). 696 (ABP 980: n = 358; TRAS: n = 338) were included in the pCR evaluable population. Based on local reviews, 48.0% and 40.5% of patients in the ABP 980 arm and TRAS arm, respectively, achieved pCR. RD and RR of pCR were 7.3% (90% CI: 1.2%, 13.4%) and 1.19 (90% CI: 1.033, 1.366), with the upper bound CI slightly exceeding the equivalence margin. Based on central independent review, 47.8% and 41.8% in the ABP 980 arm and TRAS arm achieved pCR. RD and RR of pCR were 5.8% (90% CI: 1.2%, 13.4%) and 1.36 (90% CI: 1.106, 1.69), with the upper bound CI slightly exceeding the equivalence margin. The primary endpoint was pathological complete response (pCR) at surgery. Secondary endpoints were overall response rate (ORR), PFS, and safety.

Results: The pCR rate was 46.8% in CT-P6 and 50.4% in RTZ. The 95% CIs for the estimate of treatment difference were within the equivalence margin (±9.15) in both PPS and ITT. The proportion of patients with at least 1 SAE was 7.4% in CT-P6 and 11.9% in RTZ over 1-year treatment. 6 patients (3 in CT-P6 and 3 in RTZ) withdrew treatment due to significant LVFE decrease. Inclusion related reactions was reported for 11.4% of patients in CT-P6 and 10.4% of patients in RTZ.

Table: 152PD Summary of efficacy endpoints

<table>
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<th></th>
<th>PPS</th>
<th>ITT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>pCR (ypT0/is ypN0)</strong></td>
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</tr>
<tr>
<td>pCR rate</td>
<td>46.8</td>
<td>50.4</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(40.4 – 53.2)</td>
<td>(41.1 – 56.7)</td>
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<tr>
<td>Difference estimate</td>
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<td>-0.0358</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(-0.1238 – 0.0516)</td>
<td>(-0.1198 – 0.0480)</td>
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<tr>
<td><strong>ORR (independent review)</strong></td>
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<tr>
<td>ORR</td>
<td>88.3</td>
<td>89.5</td>
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<tr>
<td>(95% CI)</td>
<td>(83.6 – 92.0)</td>
<td>(85.0 – 92.9)</td>
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<td>Difference estimate</td>
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<td>-0.0070</td>
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<tr>
<td>(95% CI)</td>
<td>(-0.0990 – 0.0764)</td>
<td>(-0.0911 – 0.0769)</td>
</tr>
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</table>

Conclusions: This study demonstrated the equivalence of efficacy between CT-P6 and Reference Trastuzumab in EBC patients. Secondary efficacy endpoints also supported the similarity for two study drugs. CT-P6 was well tolerated with a similar safety profile to that of Reference Trastuzumab through the neoadjuvant and adjuvant period.
One-year safety, immunogenicity, and survival results from a phase III study comparing SB3 (a proposed trastuzumab biosimilar) and originator trastuzumab in HER2-positive early breast cancer treated with neoadjuvant-adjuvant treatment


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Background: Equivalence for efficacy between SB3 (a proposed trastuzumab biosimilar) and originator trastuzumab (TRZ) in terms of breast pathologic complete response (bpCR) rates has been demonstrated and previously reported. Here we present the one-year results on safety, immunogenicity, event-free-survival (EFS), and overall survival (OS).

Methods: Study compared neoadjuvant SB3 or TRZ for 8 cycles concurrently with chemotherapy (4 cycles of docetaxel followed by 4 cycles of 5-fluorouracil/epirubicin/ cyclophosphamide). Patients then underwent surgery followed by 10 cycles of adjuvant SB3 or TRZ as randomised. The primary endpoint was bpCR rate and secondary end-points included safety, immunogenicity, EFS, and OS up to the adjuvant period.

Results: A total of 875 patients were randomised with a median follow-up duration of 438 days, and 765 patients completed adjuvant therapy (SB3, N = 381; TRZ, N = 384). Incidences of treatment emergent adverse events (TEAEs) were comparable between arms (Table). Most frequently occurring TEAEs were alopecia, neutropenia, and nausea during the neoadjuvant period and radiation skin injury, procedural pain, and fatigue during the adjuvant period. EFS rates were 92.2% in SB3 and 91.6% in TRZ (hazard ratio 0.94; 95% CI, 0.59 to 1.51). There were a total of 6 deaths (SB3, N = 1; TRZ, N = 5). Immunogenicity was low and comparable, with anti-drug antibody positivity for 3 patients (0.7%), in each arm.

Conclusions: One-year safety, immunogenicity, and survival results further support the biosimilarity established between SB3 and TRZ. Reference: 1. Pivot X et al. ASCO 2017, ID509

Clinical trial identification: EudraCT Number: 2013-004325-84 NCT Number: NCT02162667

Legal entity responsible for the study: Celltrion, Inc.

Funding: Celltrion, Inc.


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A randomized, double-blind study of PF-05280014 (a potential biosimilar) vs trastuzumab, both given with docetaxel (D) and carboplatin (C), as neoadjuvant treatment for operable human epidermal growth factor receptor 2-positive (HER2+ ) breast cancer

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Background: This comparative clinical trial evaluated efficacy, safety, immunogenicity and pharmacokinetics (PK) of PF-05280014, a potential trastuzumab biosimilar, vs trastuzumab sourced from the EU (trastuzumab-EU), both given with D and C, as neoadjuvant treatment for operable HER2+ breast cancer.

Methods: Patients (pts; N = 226) were stratified by primary tumor size and hormone receptor status and randomized 1:1 to receive PF-05280014 or trastuzumab-EU (8 mg/kg at Cycle 1; 6 mg/kg thereafter), both with D (75 mg/m²) and C (target AUC 6), every 3 weeks for 6 treatment cycles. The study was powered to test whether PF-05280014 was noninferior to trastuzumab-EU in the percentage of pts with Cycle 5 Ctrough (pre-dose Cycle 6) >20 µg/mL. Efficacy was measured by the percentage of pts with pathological complete response (pCR), defined as the absence of invasive neoplastic cells in breast and lymph nodes after neoadjuvant therapy, and objective response rate (ORR). Safety and immunogenicity were also assessed.

Results: The percentage of pts with Cycle 5 Ctrough >20 µg/mL was 92.1% for PF-05280014 and 92.0% for trastuzumab-EU: 6 (12.5%) pts received postoperative trastuzumab-EU. The pCR rate was 47.0% (95% CI: 39.0-61.0) for trastuzumab-EU. Central radiology review-assessed ORR was 88.1% (95% CI: 80.2-93.7) for PF-05280014 and 82.0% (95% CI: 72.5-89.4) for trastuzumab-EU. All causality, grade 3-4 treatment-emergent adverse events were reported by 38.1% (PF-05280014) vs 43.5% (trastuzumab-EU) of pts. No pts in the PF-05280014 and 1 (0.8%) in the trastuzumab-EU group had positive anti-drug antibody titer.

Conclusions: PF-05280014 demonstrated similar efficacy, safety and immunogenicity, and noninferiority in PK to trastuzumab-EU. A separate comparative safety and efficacy study (NCT01989676) is evaluating PF-05280014 vs trastuzumab-EU, both given with paclitaxel, as first-line treatment for HER2+ metastatic breast cancer.

Clinical trial identification: NCT02187744; EudraCT No: 2013-004679-11

Legal entity responsible for the study: Pfizer Inc.

Funding: Pfizer Inc.

Disclosure: P.E. Lammers: Advisory boards with Pfizer Inc. M. Dank: Member of Biosimilars Oncology European Advisory Board with Pfizer Inc since 2013. R. Abbas, F. Hilton, J. Caardo, I. Jacobs: Full-time employee and/or stock options from Pfizer Inc. All other authors have declared no conflicts of interest.

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Table: 153PD Safety profile

<table>
<thead>
<tr>
<th>SB3 N = 437 n (%)</th>
<th>TRZ N = 438 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of TEAEs</td>
<td>426 (97.5)</td>
</tr>
<tr>
<td>Grade ≥ 3 TEAEs</td>
<td>325 (74.3)</td>
</tr>
<tr>
<td>TEAEs of special interest*</td>
<td>48 (11.0)</td>
</tr>
<tr>
<td>Serious TEAEs</td>
<td>56 (12.8)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>

*Includes infusion-related reaction, left ventricular systolic dysfunction, and congestive heart failure.
Background: Increased number of TILs at baseline is associated with pathological complete response (pCR) and improved outcomes in HER2+ early breast cancer (BC) treated with anti-HER2-based chemotherapy. The associations in the neoadjuvant setting in the absence of chemotherapy and the effect of on-treatment TILs changes on pCR in the breast (pCRB) are unknown.

Methods: PAMELA is a prospective study in HER2+ BC designed to evaluate the ability of the PAM50 intrinsic subtypes (IS) to predict pCR following neoadjuvant lapatinib and trastuzumab (with hormonal therapy if hormone receptor-positive [HR+]). Levels of TILs at continuous and categorical (TILs-low < 50%, TILs-high > 50%) variables and their changes were correlated with pCRB.

Results: TILs evaluation was available for 148 baseline (BS) and 134 Day-15 (D15) samples of 151 recruited patients. At BS, the median (interquartile range) levels of TILs were 10% (5-20). Median TILs distribution according to IS was: HER2-E (10%), Lum A (17.5%), Lum B (5%), Basal-like (5%) (p < 0.02). Levels of TILs were higher in HR- (10%, 1-20) vs HR+ (5%, 1-20) tumors, although not statistically significant (p = 0.07). pCR rates were 38.5% (7/18) for TILs-high and 27.2% (37/135) for TILs-low (p = 0.03). At baseline, TILs were significantly associated with pCR in uni-variate analysis. At D15, median levels of TILs were 15% (5-30) with an increase across all the different subtypes (p < 0.01). The distribution of TILs-low (< 50%) and TILs-high (> 50%) at D15 and changes of TILs levels from BS to D15 were associated with higher pCR rates independently of HR status and IS (p < 0.01). When analysis was performed for HR-negative and HR-positive patients, separately in both cohorts, TILs at D15 was significantly associated with pCR.

Conclusions: The presence of TILs at D15 is an independent predictive marker of pCR in HER2+ early BC treated with neoadjuvant anti-HER2 agents without chemotherapy.

Clinical trial identification: NCT01973660

Legal entity responsible for the study: SOLIT Breast Cancer Research Group

Funding: GlaxoSmithKline (now Novartis)

Disclosure: All authors have declared no conflicts of interest.

155PD 10 years follow up of the RASTER study: implementing a genomic signature in daily practice


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Background: In 2004 the 70-gene signature, MammaPrint® (MP), developed to predict High or Low Risk of distant breast cancer (BC) recurrence, was introduced in the observational RASTER trial. Patients (cT1–3N0M0) and their doctors took the clinical risk assessment, which did not accurately identify high-risk patients. In contrast to genomic risk stratification, the clinical risk assessment was unable to differentiate for survival between ER+ Risk patients.

Methods: Ten year survival data was available for all 427 Raster patients, age < 61. For the current analysis, clinical high (C-high) or low (C-low) risk was scored according to the modified version of Adjuvant Online (Cardoso, N Engl J Med, 2016). 10-year distant recurrence-free interval (DRFI) probabilities were compared between risk groups based on the 70-gene signature and clinical assessment.

Results: The 70-gene signature identified 51.4% (219/427) patients with a genomic Low Risk of BC recurrence (G-low). 10-year DRFI in patients with G-low or genomic High Risk (G-high) was 93.7% and 86.8% respectively (HR 1.4; 95% confidence interval [CI] 1.0-1.9). Clinical assessment identified 57% as C-low. The 10-year DRFI was 91.3% in C-low and 88.2% in C-high (HR 1.4; 95%CI 0.8-2.6). The 10-year DRFI in the combined genomic and clinical risk groups was 94.4% in patients with a C-low/G-Low profile, only 11.6% of them received AST. In the C-low/G-High 10-year DRFI was 88.5% over 90% of them received AST. For C-high risk patients 10-year DRFI was 90.9% if G-Low (n = 46) and 87.3% if G-high (n = 137). In ER-positive BC (ER+) (N = 342) 10-year DRFI was 93.6% (G-Low) versus 88.8% (G-High) (HR 1.6; 95%CI 0.8-3.3). With clinical risk assessment, 10-years DRFI in ER+ was 91.6% (C-low) versus 91.9% (C-high).

Conclusions: Patients who omitted chemotherapy based on MammaPrint Low Risk had an excellent 10 year DRFI, confirming the prognostic value of the MP (Dukker, Int J Cancer, 2013). In this analysis we report the outcome at 10 years.

Methods: The US010622 study failed to show a benefit for the addition of capcitabine to adjuvant chemotherapy (O’Shaughnessy J. et al. 2015). Arms were pooled and DNA and RNA were extracted from 1,181 tumor samples, of which 145 patients had a DFS event, and were matched demographically to a set of 146 patients without an event for targeted NGS profiling using FoundationOne®. Gene expression was previously run using a breast cancer specific 800-gene panel (Wilson T.R. et al. 2016).

Results: Analysis of somatic alterations within IHC subtypes identified unique prognostic factors, e.g. alterations in ATM, ERCC4 and RGR2 correlated with a worse HR in HR+ disease, whereas alterations in MAP3K1, RPTOR and LYN correlated with a worse HR in TNBC. Analysis of tumor mutational burden (TMB) revealed TNBC tumors had the highest burden, which did not correlate with clinical outcomes or expression of PD1L and CD8 genes. Molecular subtyping of TNBC (Lehman B.D. et al. 2011) found distinct genetic drivers in each subtype, e.g. alterations in TP53 and MYC were the most frequent in BL2 and BL1 tumors. DM tumors expressed alterations in TP53, CEBBPP and RORC. LAR tumors expressed alterations in FN1 and A2M.

Conclusions: TMB was not prognostic and did not correlate with PD1L or CD8 gene expression, suggesting that TMB in TNBC may not be a surrogate for the immune acti-vated subtype. TNBC molecular subtyping identified different genomic drivers providing evidence for genomic heterogeneity within subtypes. Lastly, comparison of patients that experienced a DFS event identified genomic alterations that may be used to identify high-risk patients.

Clinical trial identification: Patients were enrolled onto the parent study US010622, (NCT00809479).

Legal entity responsible for the study: Hoffmann-La Roche

Funding: Genentech, Inc


Stocks in Roche
Background: In premenopausal pts with HER2+ EBC, the prognostic effect of TIA is unknown and the gonadotoxicity of trastuzumab (T) and lapatinib (L) remains largely uncertain. We aimed to assess the prognostic effect of TIA and the impact of T and/or L on the risk of developing TIA in premenopausal pts with HER2+ EBC.

Methods: ALTTO was an international, open-label, randomised phase 3 trial in pts with HER2+ EBC. Pts were randomised in 4 adjuvant anti-HER2 arms: T alone, L alone, a sequence of the 2 agents (T-L), and their combination (T-L). As per study protocol, menopausal status was collected in all pts at randomisation and at week 37. By selecting only premenopausal pts at randomisation, we investigated whether TIA in pts with hormone receptor-positive (HR+) and negative (HR-) EBC would impact on disease-free (DFS) and overall survival (OS), and the risk factors for developing TIA. Landmark and time-dependent modeling were used to account for guaranteed time bias.

Results: Out of 8381 pts randomised in ALTTO, 2862 were included in this analysis. Median age was 43 years (range 38-47); 1679 (59%) pts had HR+ EBC Pts with HR+ HER2+ EBC who experienced TIA had significant better DFS (hazard ratio (HR) 0.64; 95% confidence intervals (CI) 0.52-0.79) and ON (HR 0.53; 95% CI 0.38-0.74) than those who did not have TIA. By contrast, pts with HR-/HER2+ EBC had similar DFS (HR 0.85; 95% CI 0.68-1.07) and OS (HR 0.89; 95% CI 0.64-1.25) regardless of whether they had TIA (interaction for DFS 0.099 and for OS 0.092). A similar TIA rate was observed in the (72.6%), L (74.0%), T-L (<0.001), and T-L arms (p = 0.644). Older age (p < 0.001), addition of taxanes to anthracycline-based chemotherapy (p = 0.01) and use of adjuvant endocrine therapy (p = 0.01) significantly increased the risk of TIA.

Conclusions: In premenopausal pts with HR+/HER2+ EBC, TIA was associated with significant survival benefits. Anti-HER2 agents did not impact the likelihood of developing TIA. These data are of great importance in oncofertility counseling and support the use of ovarian suppression as part of adjuvant endocrine therapy in premenopausal HR+/HER2+ EBC pts.

Clinical trial identification: The trial is registered with the clinicaltrial.gov identifier, number NCT01040139.

Legal entity responsible for the study: Novartis Pharma AG, Basel, Switzerland

Funding: Novartis Pharma AG and the National Cancer Institut of the National Institutes of Health.

Disclosure: E. De Azambuja: Honoraria from Roche. Travel grants from Roche and GlaxoSmithKline outside the submitted work. All other authors have declared no conflicts of interest.

Table: 159PD Summary of response

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (6-cycle TChbP)</th>
<th>Group B (4-cycle TChbP switched to 4-cycle TDM1+P)</th>
<th>Group C1 (4-cycle TDM1+P continued 2-cycle TDM1+P)</th>
<th>Group C2 (4-cycle TDM1+P switched to 4-cycle FEC)</th>
<th>Group C (n = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR rate</td>
<td>Overall</td>
<td>56.9 (29/51)</td>
<td>71.2 (37/52)</td>
<td>62.5 (50/80)</td>
<td>38.1 (8/21)</td>
</tr>
<tr>
<td>pCR rate, ER (+)</td>
<td>76.2 (16/21)</td>
<td>73.9 (17/23)</td>
<td>72.2 (26/36)</td>
<td>33.3 (2/6)</td>
<td>66.7 (28/42)</td>
</tr>
<tr>
<td>pCR rate, ER (+)</td>
<td>43.3 (13/30)</td>
<td>69.0 (20/29)</td>
<td>54.5 (24/44)</td>
<td>40.0 (6/15)</td>
<td>50.8 (30/59)</td>
</tr>
<tr>
<td>ORR</td>
<td>96.1 (49/51)</td>
<td>86.5 (45/52)</td>
<td>88.8 (70/80)</td>
<td>85.7 (18/21)</td>
<td>88.1 (89/101)</td>
</tr>
<tr>
<td>cCR</td>
<td>47.1 (24/51)</td>
<td>51.9 (27/52)</td>
<td>38.8 (31/80)</td>
<td>38.1 (8/21)</td>
<td>38.6 (39/101)</td>
</tr>
<tr>
<td>Breast conservation rate</td>
<td>52.0 (26/50)</td>
<td>51.9 (27/52)</td>
<td>54.4 (43/79)</td>
<td>38.1 (8/21)</td>
<td>51.0 (51/100)</td>
</tr>
<tr>
<td>Breast conservation rate from planned mastectomy</td>
<td>34.4 (11/32)</td>
<td>38.7 (12/31)</td>
<td>36.7 (18/49)</td>
<td>14.3 (2/14)</td>
<td>31.7 (20/63)</td>
</tr>
</tbody>
</table>

Dose was administered every 3 weeks as adjuvant therapy. ER (+) patients received concurrent endocrine therapy during TDM1 treatment. ER, estrogen receptor; FEC, 5-fluorouracil/epirubicin/cyclophosphamide; ORR, overall response rate; pCR, pathological complete response; TChbP, docetaxel/carboplatin/trastuzumab + pertuzumab; TDM1+P, trastuzumab emtansine + pertuzumab
post-menopause 53.9%, T2 70.6%, median tumor size 26 mm, N0 63.2%, ER(+) 57.8%. In group C, 79.7% patients continued T-D1-M1-P due to favorable response. Pcr rate in group A, B, and C was 56.9%, 71.2%, and 57.4%. By exploratory analysis, pCR rate was higher for groups B and C than A in ER(+), but comparable in ER(-) patients. No significant differences in secondary endpoints. No treatment discontinuation due to AEs and similar drug-related SAE profile were seen among groups. Of specific mention: low drug-related alopecia in group C (3.0%) than A, B or C (81%-94%) and less febrile neutropenia in C (9%) than A, B or C (15%-33%).

Conclusions: Addition of T-D1-M1-P to standard TCHP regimen may be possibly superior to TCHP. Tailored T-D1-M1-P is a promising approach with mostly equal efficacy and less toxicity compared to TCHP.

Clinical trial identification: UM1112378774 (TCHP),UM1112378773 (TCHP-A) ,UM1112378775 (TCHP-B), UM1112378776 (TCHP-C)

Legal entity responsible for the study: ICM Regional Cancer Center of Montpellier

Funding: French National Institute of Cancer (INCa)

Disclosure: All authors have declared no conflicts of interest.
Background: Patients (pts) with TNBC involved in the GeparSixto study showed an improved pCR rate ( ypT0 ypN0) with the addition of carboplatin (Cb) to anthracycline/taxane-based neoadjuvant chemotherapy, which translated in an improved pCR rate (ypT0 ypN0) with the addition of carboplatin (Cb) to anthracycline/taxane-based neoadjuvant chemotherapy, which translated in an improved early disease-free survival (DFS). No difference was observed in the HER2 subgroup for pCR and DFS by adding Cb. Here, we present the results on the long-term survival analysis.

Methods: In the GeparSixto trial, pts were treated for 18 weeks with paclitaxel 80mg/m² q2w and non-pegylated-liposomal doxorubicin (NPLD) 20mg/m² q1w (PM), con- sequently with bevacizumab 15mg/kg q1w of TNBC or trastuzumab 6mg/kg q2w and lapatinib 750mg daily (if HER2 –). 595 pts were randomized 1:1 to receive concurrently Cb AUC 1.5–2.0 q2w (reduced to 1.5 by an amendment after 330 pts) vs no Cb, stratified by subtype (HER+ vs TNBC). 588 pts started treatment. Primary objective was pCR ( ypT0 ypN0), DFS, distant DFS, loco regional recurrence-free (LRFS) and overall survival (OS). Cb was used in 320 pts.

Results: After a median follow-up of 47.3 months (range 1.7-62.8) overall no significant difference in DFS was seen in PMCb vs PM (HR = 0.83 [95% CI 0.58-1.20]; p = 0.327). However, Pts with TNBC had a significantly better DFS (HR = 0.56 [95% CI 0.34-0.93]; p = 0.024) and DDFS (HR = 0.50 [95% CI 0.29-0.86]; p = 0.013) when treated with PMCb. No difference was seen in pts with HER2+ disease (DFS HR = 1.34 [95% CI 0.77-2.34]; p = 0.295; interaction test p = 0.022 and DDFS HR = 1.56 [95% CI 0.86-2.83]; p = 0.145; interaction test p = 0.006). A trend towards a better OS was observed in pts with TNBC (HR = 0.60 [95% CI 0.32-1.12]; p = 0.110). OS was not different between the two arms, neither overall (HR = 0.72 [95% CI 0.43-1.21]; p = 0.246) nor HER2+ disease (HR = 1.13 [95% CI 0.44-2.91]; p = 0.800). Multivariable analysis confirms that Cb decreases DFS and DDFS, while Cb did not affect RRFS or OS.

Conclusions: Long-term survival analysis supports the neoadjuvant use of Cb in TNBC. The value of Cb as a strong predictor of DFS and OS was confirmed.

Clinical trial identification: NCT 01426880

Legal entity responsible for the study: German Breast Group

Funding: Teva, GSK, Roche, Hexal

Disclosure: G. von Minckwitz, S. Loibl: Research grant to the institution from Teva. All authors have declared no conflicts of interest.

164P Impact of lack of surgery on outcomes in elderly patients with non-metastatic breast cancer (BC): A population based study using the SEER 18 data base

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Background: Elderly women with non-metastatic BC do not always receive standard of care definitive surgical treatment. Both provider and patient related reasons have been cited. The impact of omitting surgery in elderly patients who otherwise would be candidates for surgery has not been addressed. We performed a population based study to evaluate the impact of lack of surgery on survival outcomes in elderly women with BC in modern era.

Methods: The Surveillance, Epidemiology and End Results database was queried from 2010 to 2013 for female patients age 60 and older with a diagnosis of invasive ductal or lobular BC with AJCC stage I, II, III. To determine the relationship between surgery at diagnosis and survival and to take into consideration the effect of comorbidities, we organized patients in the following groups: a. Surgery performed, b. Surgery recommended, but not performed; c. Surgery not recommended and not performed. The Kaplan–Meier method was used to generate survival curves and the log-rank test was performed to compare OS rates among different groups.

Results: 119,404 patients were eligible with a median age between 70 to 74 years old. 71,638 (60%) patients were stage I, 37,524 (31.42%) were stage II and 10,245 (8.58%) were stage III. 85.2% were ER +, 12.4% were Her 2 + and 8.8% were triple negative (TN). Compared with the patients who received surgery, patients who did not receive surgery had a significantly worse outcome (all patients: HR = 7.39, 95% CI 6.98–7.83, P < 0.001. Patients who were recommended to have surgery but did not receive it had significantly worse survival than patients who underwent surgery (HR = 5.08, 95% CI 4.86–5.76, P < 0.001) although better OS than those who were recommended against surgery (HR = 0.62, 95% CI 0.54–0.71, P < 0.001). Similar results were found in subgroup analyses regardless of age, tumor stage, ER or HER2 status. Patients with TNBC who did not received surgery also had a significantly worse OS than those who received surgery. (HR = 4.89, 95% CI 4.07–5.88, P < 0.001).

Conclusions: Definitive surgery should be performed in medically-fit elderly patients with non-metastatic BC due to a significant survival benefit.

Legal entity responsible for the study: Cristina Truica

Funding: None

Disclosure: All authors have declared no conflicts of interest.

167P Time to surgery in early breast cancer treated with neoadjuvant chemotherapy

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Background: A delay between surgery and adjuvant chemotherapy (CT) has been associated with worse outcome in early breast cancer (BC), but little is known about timing-related consequences in the neoadjuvant setting. Aim of this study is to investigate the impact of the interval between the end of neoadjuvant CT and surgery (CTTS).

Methods: This retrospective study analyzed a series of 469 consecutive BC patients (pts) receiving neoadjuvant CT at the Department of Oncology of Udine (n = 222) and of the Istituto Nazionale Tumori of Milan (n = 247), between 2004 and 2015.

CTTS
Introduction: TNBC has the highest mortality of all BC subtypes. Neoadjuvant platinum added to neoadjuvant dose dense paclitaxel (P) followed by inipirubicin (E) and cyclophosphamide (C) in triple negative breast cancer (TNBC) patients (pts)

Methods: Patients and methods: Sixty three pts received dose dense P (80mg/m2/wk) concurrent with C (AUC=2) for 12 wks, added to two weekly E (90mg/m2) and G (600mg/m2) for 4 cycles, and followed by surgery and radiotherapy. The primary end-point was PCR in the breast and axilla. Additionally adverse events are registered. A correlative assessment of germ line mutations in BRD genes is ongoing. Pts are monitored for clinical response by magnetic resonance imaging and mamography and also for relapse free survival and time to treatment failure. The study sample size has been calculated according to the optimal Simon’s two-stage design method. The target sample size was 63 patients with 80% power to detect a PCR rate of ≥ 47% (α = 0.05).

Results: Accrual to the study is completed and 63 eligible pts with operable, non-inpreatory stage II/III TNBC pts. Most pts were between 40 and 60 yr old and 49 out of 63 were stage 2. Forty percent were clinically node + and 66% were T3. Twenty three percent received breast conservaing surgery. Thirty eight out of 63 pts (60%) achieved a PCR rate in the breast and axilla. In 52 evaluable pts for toxicity, the main toxicity for part 1 (Cp + E) was neutropenia G3/4 in 18 pts (34%) despite primary prophylaxis, followed by thrombocytopenia G3/4 in 11 pts (21%). Only three pts had a neuropathy G3.

Conclusions: The addition of weekly carboplatin to neoadjuvant dose dense paclitaxel and EC is feasible and a PCR rate in the breast and axilla as high as 60% in early TNBC pts is obtained. Correlation with genomic HRD deficiency is ongoing.


Legal entity responsible for the study: Breast Cancer Task force on behalf of the BSMO (Belgian Society of Medical Oncology).

Funding: Amgen and Teva

Disclosure: All authors have declared no conflicts of interest.
Composite index of risk shows that benefit from adjuvant dose dense chemotherapy is not confined to triple negative breast cancer

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Background: A randomized phase III GM2 trial enrolled 2091 pts with node-positive breast cancer (EBC) patients (pts). To date, GIM2 is the only trial supporting the role of dose-dense chemotherapy in pts with hormone receptor-negative (HR-) or hormone receptor-positive tumours (HR +) (Del Mastro et al. Lancet 2015). To further refine the evidence of treatment effect in the HR + subgroup, a composite index of risk was developed including clinico-pathological features.

Methods: The randomized phase III GM2 trial enrolled 2091 pts with node-positive breast cancer (EBC) patients (pts). To date, GIM2 is the only trial supporting the role of dose-dense chemotherapy in pts with hormone receptor-negative (HR-) or hormone receptor-positive tumours (HR +) (Del Mastro et al. Lancet 2015). To further refine the evidence of treatment effect in the HR + subgroup, a composite index of risk was developed including clinico-pathological features.

Results: On average, the magnitude of benefit with dose dense chemotherapy versus standard chemotherapy widely varied according to composite measure of specific features. In the HER2- subgroup, the highest benefit was observed in pts with G3, HR+, >10 positive nodes, age >40 yrs, ki-67 >20% (hazard ratio for DFS 0.57, 95% CI 0.35-0.94). Notably, among pts with HR + disease, the following clinic-pathological characteristics conferred the highest benefit: G3, ≤2 positive nodes, age ≥56 yrs, ki-67 >20% (hazard ratio for DFS 0.46, 95% CI 0.38-1.15).

Conclusions: Composite risk evaluation and corresponding subpopulation treatment effect pattern methodology suggest that benefit of dose dense adjuvant chemotherapy is not confined to triple negative EBC.

Legal entity responsible for the study: Gruppo Italiano Mammella

Funding: None

Disclosure: All authors have declared no conflicts of interest.

The prognosis of chemotherapy induced amenorrhea in women treated with early stage breast cancer

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Background: In this study, Amenorrhea caused by chemotherapy in early stage breast cancer patients and its effects on survival were investigated.

Methods: A total of 389 pts who received adjuvant chemotherapy from 600 premenopausal pts that were treated with early stage breast cancer during 2008-2013 and followed up were included in the study. Patients who did not undergo medical ovarian ablation (OA). Amenorr as developing and non-developing, two groups were separated and compared with clinicopathologic features and survival. SPSS 17. version was used.

Results: Disease-free survival (DFS): median (m) 57 months (4-197 months), overall survival (OS): m 60 (10-168 months) and follow up time m 60 months (23-168 months). During follow-up, chemotherapy induced amenorrhea (CIA) was observed in 145 (37.9%) of 352 pts who did not have any ovarian ablation (OA). The 5-Year OS rate of patients with CIA was significantly higher than the patients without CIA (p = 0.042, 95% CI vs 89.7 vs 158.68 vs 135.33 months, respectively). In the subgroup analysis, the OS in pts with CIA was significantly higher than in those without CIA in patients with HR + (p = 0.036, 97.5% vs 91.5 % vs 162.13 vs 136.20 months, respectively). There was no significant difference in the duration of OS between CIA and without CIA of the patients who had HR + ( p = 0.736, 90.9% vs 86.8% and 126.16 and 133.76 months, respectively). The duration of OS was significantly longer in patients with CIA in the luminal A molecular subtype than in those luminal B molecular subtype, but the difference was not significant in patients without CIA ( p = 0.027 vs p = 0.074 respectively).

Conclusions: The development of amenorrhea due to chemotherapy provides a significant survival advantage over those patients who do not develop amenorrhea due to chemotherapy. This advantage is more pronounced in hormone receptor positive, lymph node involvement and advanced disease. The development of amenorrhea due to chemotherapy in patients with HR negative does not affect survival. Amenorrhea development further prolongs survival compared to luminal B in the luminal A molecular subtype.

Legal entity responsible for the study: Istanbul Bilim University, Florence Nightingale Group of Hospitals

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Determinants and outcomes associated with delays in adjuvant chemotherapy among breast cancer patients

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Background: Adverse outcomes have been associated with delays in the administration of adjuvant chemotherapy among breast cancer patients. We evaluate the determinants and outcomes associated with delays in time to chemotherapy (TTC) in a large cohort of older breast cancer patients.

Methods: We used the NCIL-Surveillance Epidemiology and End Results (SEER) and Texas Cancer Registry (TCR)-Medicare linked data bases to identify patients ≥66 years old diagnosed with localized or regional breast cancer between 2001-2011. All patients received chemotherapy within 9 months of surgery. Delayed TTC was defined as ≥ 90 days. Multivariable logistic regression was used to identify predictors of treatment delay. A Cox Proportional Hazards model was fit to determine the association between treatment delay, overall survival (OS) and breast cancer specific survival (BCSS).

Results: 25,096 patients were included, of them 2,676 (10.7%) had a TTC ≥90 days. In multivariable analysis factors associated with delays in TTC were: recent year of diagnosis (2011 vs 2001 OR = 1.31; 95%CI 1.01-1.67), older age (76-80 vs 60-69 OR = 1.51, 95%CI 1.33-1.72), Black race (OR = 1.35; 95%CI 1.14-1.56), having state buy-in (as an indicator of poverty) (OR = 1.27; 95%CI 1.1-1.47), comorbidities (Charlson score 1 OR = 1.23;95%CI 1.09-1.37, score 2 OR = 1.57; 95%CI 1.37-1.81), mastectomy (OR = 1.49; 95%CI 1.33-1.67), mastectomy (OR = 1.85; 95%CI 1.37-2.48), Oncotype DX testing (OR = 1.68; 95%CI 1.4-2.02), mastectomy >30 days after the initial surgery (OR = 16.91; 95%CI 12.07-23.68), brachytherapy (OR = 4.11, 95%CI 3.17-5.34) and whole breast radiation prior to
174P Adjuvant chemotherapy in pT1ab node-negative triple negative breast carcinomas: Results of a national multi-institutional retrospective study

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1Medical Oncology, Institut Paoli Calmettes, Marseille, France, 2Surgeical Oncology, Institut Paoli Calmettes, Marseille, France, 3Surgical Oncology, Institut René Gauducheau, Saint Herblain, France, 4Surgical Oncology, Institut Curi, Pain, France, 5Surgical Oncology, Val-d’Aurel, Montpellier, France, 6Surgical Oncology, Institut Claudius Regaud, Toulouse, France, 7Surgical Oncology, Centre Oscar Lambret, Lille, France

Background: Triple negative breast cancers (TNBC) are considered as associated with poor outcome, but prognosis of subcentimetric, node-negative disease remains controversial and evidence that adjuvant chemotherapy (CT) is effective in these small tumors remains limited.

Methods: Our objective was to investigate the impact of adjuvant CT on survival in pT1abN0M0 TNBC. Patients were retrospectively identified from a cohort of 22,475 patients who underwent primary surgery in 15 French centers between 1987 and 2013. Since rare pathological types may display very particular prognoses in these tumors, we retained only the invasive ductal carcinomas of no special type according to the last WHO classification which is most common TNBC histologic type. End-points were disease-free survival (DFS) and metastasis-free survival (MFS). A propensity score for receiving CT was estimated using a logistic regression including age, tumor size, SBR grade, and lymphovascular invasion.

Results: Of a total of 284 patients with pT1abN0M0 ductal TNBC, 144 (51%) received post-operative CT and 140 (49%) did not. Patients receiving CT had more adverse prognostic features, such as tumor size, high grade, young age, and lymphovascular invasion. Adjuvant CT was not associated with a significant benefit for DFS (Hazard ratio, HR = 0.77; 0.40-1.46; p = 0.419, Log rank test) or MFS (HR = 1.00 [0.46-2.19], p = 0.997), with 5-year DFS and MFS in the group CT vs. without of 90% (81%-94%) vs. 84% (74%-90%), and 90% (81%-95%) vs. 90% (83%-95%), respectively. Results were consistent in all supportive analyses including multivariate Cox model and the use of the propensity score for adjustment and as a matching factor for case-control analyses.

Conclusions: This study did not identify a significant DFS or MFS advantage for adjuvant CT in subcentimetric, node-negative ductal TNBC. Although current consensus guidelines recommend consideration of adjuvant CT in all TNBC larger than 5 mm, clinicians should carefully discuss benefit/risk ratio with patients, given the yet unproven benefits of CT.

Legal entity responsible for the study: SIRIC program (InCa-DGOS-Inserm 6038)

Funding: SIRIC program (InCa-DGOS-Inserm 6038)

Disclosure: All authors have declared no conflicts of interest.

175P OHERA: A real world study of cardiac events in > 3700 patients with her2-positive early breast cancer treated with trastuzumab: Final analysis

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Background: Breast cancer patients in low and middle income countries have limited access to targeted therapies such as trastuzumab. The discontinuous availability of trastuzumab created waiting lists and subsequent very delayed treatment. Since few studies have systematically analyzed possible deleterious effect of delayed trastuzumab treatment, we designed a study to investigate its consequences on overall survival and disease-free survival.

Methods: This was a multicenter cohort study of HER2-positive early breast cancer patients (n = 223) diagnosed between 01/05/2005 and 01/05/2010 in the Federation of Bosnia and Herzegovina. The study began in 01/01/2010, and enrollment was completed in 03/06/2012. Last follow-up and cut off date for analysis was 31/03/2015. Results: A total of 223 women (median 55 years; IQR: 49-61 years) were recruited. Since 131 (99%) patients waited for > 6 months after surgery to receive trastuzumab, we categorized our patient cohort into three groups: non-waiting group (n = 92; wait time < 6 months), and waiting group 1 (n = 85; wait time between 6 to 12 months) and waiting group 2 (n = 46; > 13 months wait). OS at 5 years in non-waiting group was 84%, compared to 72% in wait group 1 and 75% in wait group 2 ( p < 0.05). DFS at 5 years in the non-wait group was 79%, compared to 65% in wait group 1, and 68% in wait group 2 (p < 0.05).

Conclusions: Unfortunate and unique circumstances in developing countries have created waiting lists for trastuzumab treatment—our systematic analysis of 223 women has shown that delayed start of trastuzumab treatment does not have a statistically significant effect on clinical outcomes, but shows a trend towards worse OS and DFS for women with delayed treatment. Thus, trastuzumab treatment has a persistent benefit even when administered with delayed start.

Clinical trial identification: ML25232

Legal entity responsible for the study: Roche

Funding: Roche

Disclosure: T. Ceric: Honoraria: Roche, Novartis, Pfizer. Consulting or Advisory Role: Roche, Novartis, Pfizer. All other authors have declared no conflicts of interest.

176P Clinical outcomes of delayed start of trastuzumab treatment in patients with early breast cancer: ml25232 study

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Background: Breast cancer patients in low and middle income countries have limited access to targeted therapies such as trastuzumab. The discontinuous availability of trastuzumab created waiting lists and subsequent very delayed treatment. Since few studies have systematically analyzed possible deleterious effect of delayed trastuzumab treatment, we designed a study to investigate its consequences on overall survival and disease-free survival.

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Clinical trial identification: ML25232

Legal entity responsible for the study: Roche

Funding: Roche

Disclosure: T. Ceric: Honoraria: Roche, Novartis, Pfizer. Consulting or Advisory Role: Roche, Novartis, Pfizer. All other authors have declared no conflicts of interest.
Effects of neratinib (N) on health-related quality of life (HRQoL) in early-stage HER2+ breast cancer (BC): longitudinal analyses from the phase III ExteNET trial

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Background: The international, randomized, placebo (P)-controlled phase III ExteNET trial (NCT00878709) showed that N for 1 y after trastuzumab-based adjuvant therapy significantly improved 2-y invasive disease-free survival in early HER2+ BC patients (pts) (HR 0.67; 95% CI 0.50–0.89; p = 0.0091) [Chan et al. Lancet Oncol 2016]. Detailed longitudinal evaluation of HRQoL was an exploratory endpoint of ExteNET.

Methods: 2840 pts received N 240 mg/d or P for 1 yr. Pts completed FACT-B and EQ-SD questionnaires at baseline and months (M) 1, 3, 6, 9, and 12. Changes in scores from baseline were compared between groups using ANCOVA with no imputation for missing values. Sensitivity analyses using alternative methods were applied. Changes in HRQoL scores were considered to be clinically meaningful if greater than minimal clinically important differences (MCID) reported in the literature.

Results: 2407 pts were evaluable for FACT-B (N, n = 1171; P, n = 1236), and 2427 for EQ-SD (N, n = 1186; P, n = 1241). Compliance with questionnaires exceeded 85%. N was associated with decreased HRQoL scores at M1 vs P, after which between-group differences diminished (Table). They were consistently less than MCID, except for physical well-being (PWB) subscale at M1. BC subscale (BCS) showed small improvements with N at M3–M9, all less than MCIDs. Different sensitivity methods did not alter the results.

Table: 177P

<table>
<thead>
<tr>
<th>Scale</th>
<th>MCID range</th>
<th>N vs P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>M1</td>
</tr>
<tr>
<td>FACT-B total</td>
<td>7–8</td>
<td>-2.9*</td>
</tr>
<tr>
<td>TO1-ESB</td>
<td>5–6</td>
<td>-2.6*</td>
</tr>
<tr>
<td>TO1-PFB</td>
<td>5–6</td>
<td>0.0</td>
</tr>
<tr>
<td>PWB</td>
<td>2–3</td>
<td>-2.4*</td>
</tr>
<tr>
<td>BCS</td>
<td>2–3</td>
<td>0.3</td>
</tr>
<tr>
<td>EQ-SD index</td>
<td>0.09–0.10</td>
<td>-0.02*</td>
</tr>
<tr>
<td>EQ health state</td>
<td>7–10</td>
<td>-2.7*</td>
</tr>
</tbody>
</table>

For baseline score; *Statistically significant at p < 0.05 without adjustment for multiple testing TOI = trial outcome index; PFB = PWB + functional WB + BCS; ES8 = emotional WB + social WB + BCS.

Conclusions: N was associated with decreased HRQoL, in particular in PWB, at M1, possibly due to N-related diarrhea. Based on their small magnitude, differences observed after M1 in PWB favoring P and in BCS favoring N, may not be clinically important.

Clinical trial identification: NCT00878709

Legal entity responsible for the study: Wycl and Puma Biotechnology

Funding: Puma Biotechnology


Second interim analysis of Her2Sc, a German interventional study of subcutaneous trastuzumab for HER2-positive early breast cancer in routine clinical practice

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Background: Compared with IV trastuzumab, subcutaneous trastuzumab (H2sc) showed non-inferior outcomes in the HannaH trial and was preferred by patients and healthcare professionals in the PrefHer study. The ongoing Her2Sc study (NCT01953986) is evaluating H2sc in routine clinical practice in Germany.

Methods: Pts with HER2-positive early breast cancer treated with (neo)adjuvant H2sc (investigator’s chosen regimen) in routine oncology practice between Nov 2013 and Nov 2016 were eligible. Pts could be enrolled retrospectively up to 9 wks after starting H2sc. Baseline characteristics, treatment, adverse events (AEs), clinical outcomes and quality of life (EORTC-QLQ-C20/QLQ- BR23) data are collected prospectively. Primary efficacy endpoints are pCR rate (neoadjuvant setting) and 2-year disease-free survival (adjuvant setting).

Results: At the data cut-off for the second planned interim analysis (Nov 2016), 420 of 1007 pts enrolled to date from 103 German centres had completed therapy and were eligible for analysis. The median duration of follow-up was 12.2 (range 3.3–25.8) mo. Baseline characteristics are below. The mean duration of H2sc was 8.8 mo (neoadjuvant: 9.2; adjuvant: 8.7). All-grade and grade ≥3 AEs were reported in 63% and 15% of pts, respectively. The most common all-grade AEs were fatigue (10%), diarrhoea (9%) and arthralgia (7%). AEs led to treatment interruption/withdrawal in 48 pts (11%). Only 1 of the 4 fatal AEs was considered treatment related (cardiac/respiratory failure). The pCR rate (including carcinoma in situ) in the neoadjuvant subgroup was 60.3% (95% CI 48.5–71.2). Efficacy results in the adjuvant subgroup are not mature.

Conclusions: The 60.3% pCR rate is consistent with prospective trials of IV trastuzumab and H2sc. Tolerability is as expected based on results from randomised trials. H2sc is an active, feasible and tolerable treatment for use in routine oncology practice as well as the clinical trial setting.

Clinical trial identification: NCT01953986

Legal entity responsible for the study: Roche Pharma AG

Funding: Roche Pharma AG

Disclosure: S. Kümmel: Membership on advisory board or board of directors: Roche Pharma AG.

S. Busch-Liles: Employment: Roche Pharma AG.

S. Schmidt: Membership on advisory board or board of directors: Novartis, Pfizer, Pierre-Fabre, Roche. Corporate-sponsored research: Pierre-Fabre.

All other authors have declared no conflicts of interest.
178P
Timing of initiation of trastuzumab (T) and long-term outcome of patients (pts) with early-stage (ES) HER2-positive (HER2+) breast cancer (BrCa): Impact of neo-adjuvant (NAdj) versus adjuvant (Adj) strategy

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Background: The optimal schedule of anti-HER2 Tx for HER2+ ESBrCa with respect to chemotherapy and surgery remains undefined. We performed a retrospective analysis of a large, prospectively maintained single institution data base to study the impact of treatment schedule on clinical outcome.

Methods: Our database included all pts treated with T for Stage I to III HER2+ BrCa who had a minimum follow up (FU) of 3 years. Time-to-first-T (TFT) was calculated from the date of the first diagnostic breast biopsy to the date of the first T. Pts with stage N1b and N3c or inoperable disease were excluded from the study.

Results: A total of 506 pts treated between October 2001 and March 2014 were included in the study. T was administered as part of AdjTx in 386 (76%) pts, and of NAdjTx in 119 (24%) pts. With stage TCH [docetaxel/CBDCA/T] or “TCH-like”, 119 (24%) pts underwent NAdjTx. T was administered as part of AdjTx in 386 (76%) pts, and of NAdjTx in 119 (24%) pts. The early institution of T in the NAdj cohort abolished the negative impact of LN+; thus suggesting that this should be considered the optimal Tx strategy for ES HER2+ BrCa.

Legal entity responsible for the study: Giuseppe Gullo

Funding: None

Disclosure: All authors have declared no conflicts of interest.

179P
Adjuvant endocrine treatment: Stop or continue?

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Background: There is currently a trend towards extending adjuvant endocrine treatment in higher risk breast cancer patients up to 10 years. However, a trade off has to be made between persisting side effects of endocrine treatment vs a small advantage in recurrence risk. It is not well known if patients still suffer side effects after 5 years of endocrine treatment, and if these may be reversible. Therefore, we studied the change in side effects of endocrine treatment and overall quality of life during and 3 months after cessation, in patients who completed at least 5 years of treatment.

Methods: We included 101 patients from 2 oncological practices who underwent curative treatment for breast cancer and whose adjuvant endocrine therapy ended between 2013 and 2016. Patients willing to cooperate filled out a questionnaire before and 3 months after cessation of ESBrCa.

Results: 101 patients were included. Average was 61 years. Tumors were T1-T4, N0-M0. Most patients received tamoxifen for 2-3 years, followed by an aromatase-inhibitor for 3-6 years. The main finding of this survey is that overall quality of life improved significantly after stopping endocrine therapy from 6.9 (range 4-10) to 7.7 (3-10) (p < 0.01 Wilcoxon paired rank test). 22 women improved ≥2 points. Patients who scored high on muscle aches and joint complaints improved the most.

Conclusions: Even patients who completed at least five years of endocrine treatment suffer side effects up to the end of treatment. After cessation these ameliorate in many, and this improves quality of life significantly. These findings are relevant when deciding

Table: 178P

<table>
<thead>
<tr>
<th>Parameter, No. of pts (%)</th>
<th>All pts (n = 420)</th>
<th>Neoadjuvant subgroup (n = 78)</th>
<th>Adjuvant subgroup (n = 342)</th>
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<td>52 (20–77)</td>
<td>57 (27–90)</td>
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<td>214 (63)</td>
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<tr>
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<td>110 (32)</td>
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<td>11 (3)</td>
</tr>
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<td>HER2 status by IHC</td>
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</tr>
<tr>
<td>Histological grade</td>
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<tr>
<td>1</td>
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<td>0</td>
<td>7 (2)</td>
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<td>3</td>
<td>222 (53)</td>
<td>46 (59)</td>
<td>176 (51)</td>
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<tr>
<td>Missing/unknown</td>
<td>7 (2)</td>
<td>2 (3)</td>
<td>5 (1)</td>
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<tr>
<td>Subtype*</td>
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<tr>
<td>Ductal</td>
<td>343 (82)</td>
<td>65 (83)</td>
<td>278 (81)</td>
</tr>
<tr>
<td>Lobular</td>
<td>24 (6)</td>
<td>3 (4)</td>
<td>21 (6)</td>
</tr>
<tr>
<td>Other</td>
<td>54 (13)</td>
<td>10 (13)</td>
<td>44 (13)</td>
</tr>
<tr>
<td>Positive nodal status</td>
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<tr>
<td>0</td>
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<td>Hormone receptor status</td>
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<tr>
<td>ER positive</td>
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<td>42 (54)</td>
<td>238 (70)</td>
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<tr>
<td>PgR positive</td>
<td>234 (56)</td>
<td>39 (50)</td>
<td>195 (57)</td>
</tr>
<tr>
<td>ER and PgR negative</td>
<td>127 (30)</td>
<td>31 (40)</td>
<td>96 (28)</td>
</tr>
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</table>

*One patient (adjuvant setting) recorded as both ductal and lobular. ER=oestrogen receptor; IHC=immunohistochemistry; PgR=progesterone receptor.
on extended adjuvant endocrine treatment in individual patients. Detailed analysis will be presented.

**Clinical trial identification:** Under Dutch law no obligations for protocol submission for this type of survey, only institutional approval.

**Legal entity responsible for the study:** E.W. Muller

**Funding:** None

**Disclosure:** All authors have declared no conflicts of interest.

### 181P Use and effectiveness of adjuvant ovarian function suppression (OFS) in premenopausal women with early breast cancer

A.R. Peries 1, J. Ribera 1, A. Mayer 1, M. Brito 1, A. Miranda 1, J.P. Fernandez 1, L.L. Passos-Coelho 1, T. Costa 1, J. Vaz-Luís 1

1Medical Oncology, Hospital de Santa Maria and Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal, 2Medical Oncology, Fundação Champalimaud, Lisbon, Portugal, 3Registo Oncológico Regional do Sul, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisbon, Portugal, 4Medical Oncology, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisbon, Portugal, 5Medical Oncology, Hospital de Santa Maria, Centro Hospitalar de Lisboa e Intermédios, Lisbon, Portugal, 6Medical Oncology, Hospital da Luz and Hospital de Beatriz Angela, Lisboa, Portugal, 7Department of Medicine and Unit INSERM 981, Institut Gustave Roussy, Villejuif, France

**Background:** OFS either in association with tamoxifen (TAM) or an aromatase inhibitor (AI) improved disease-free survival in young women (≤35) and in those premenopausal women at higher risk of recurrence. However, its survival benefit remains largely unknown. In this study we characterize real-world use of adjuvant OFS from 2006 to 2015 and analyze its overall survival (OS) impact.

**Methods:** Retrospective observational cohort study of premenopausal women with Stage I-III hormone receptor-positive (HR+) breast cancer treated at one of 5 large centers in Portugal and diagnosed from 2006-2015. Study outcome measures were use of OFS and OS. Pearson’s Chi² test, logistic regression and Cox proportional hazards models were used.

**Results:** Of 1717 eligible patients, 304 (17.7%) were treated with adjuvant OFS, of which 271 (15.4%) in combination with TAM and 33 (1.9%) with AI. Baseline characteristics differed by subgroups: patients treated with OFS were younger, had larger, less differentiated (grade III 16% vs 24% for OFS), more frequently HER2 positive (14% vs. 19% for OFS) tumors, and underwent more frequently mastectomy (48% vs 57% for OFS), radiotherapy (25% vs 31% for OFS) and (neo)adjuvant chemotherapy (73% vs 79% for OFS). Adjuvant OFS was used at least since 2006 with an increase in its use from 2014 onward (16% vs 1% since 2014), particularly for the combination with AI (0.4% vs 8% since 2014). In a multivariate model, characteristics associated with use of OFS included younger age and year of diagnosis >2014 (both p < 0.001). Median time on OFS was 25 mo. (interquartile range 21-27). With a median follow-up of 38 mo. (IQR: 20-66) and after controlling for age at diagnosis, staging, histologic grade, HER2 status, use of (neo)adjuvant CT, type of surgery and year of diagnosis, patients treated with OFS had a better OS when compared to those not treated with OFS (adjusted-HR 0.44 (95% CI 0.19-0.96; p = 0.040). Absolute benefit at year 5 was 2.1% (93% CI 90.8-98.9) vs 9.3% (95% CI 89.9-97.9%)

**Conclusions:** In the real-world setting, a quarter of premenopausal women with early breast cancer were already treated with adjuvant OFS in 2014. After a median follow-up of 3 years, adjuvant OFS showed an OS benefit. Legal entity responsible for the study: Hospital de Santa Maria, Centro Hospitalar de Lisboa Norte

**Funding:** None

**Disclosure:** All authors have declared no conflicts of interest.

### 182P A phase II randomised study of Adjuvant hypo-fractionated radiotherapy with concurrent vs sequential letrozole in post-menopausal women with hormone receptor positive breast cancer: Report of pulmonary toxicity and cosmetic outcome

R. Unachthy 1, D.N. Sharma 1, P. Julka 1, G.K. Rath 1

1Radiation Oncology, All India Institute of Medical Sciences, New Delhi, India, 2Medical Oncology, B.R. Ambedkar Institute Rotary Cancer Hospital (AMSH), New Delhi, India

**Background:** The sequence of hormonal therapy with adjuvant radiation (RT) is debated because of anticipated morbidity. We conducted a phase II study to evaluate feasibility and efficacy of concurrent and sequential letrozole along with hypo-fractionated RT (HFRT).

**Methods:** A total of 50 Post-menopausal women with hormone receptor-positive, Stage-I-III Breast cancer received adjuvant HFRT 42.5Gy/16fr/3weeks and were randomly assigned to either concurrent (arm A) or sequential letrozole (arm B). Letrozole was started 3 weeks before RT in the concurrent, and 3 weeks after RT in sequential group. Pulmonary toxicity was assessed by clinical examination, chest x-ray, pulmonary function tests and HRCT chest (if indicated) at baseline, at one and six months post RT. Cosmetic outcome was reported in both arms with six parameters (Table) at 6 m post RT.

**Results:** A total of 48 patients (pts) were followed up for 6 m (25 in Arm A and 23 in Arm B). None of the pts developed acute pulmonary toxicities. Mean (R) FeV1 and FVC values at baseline, 1 and 6 m post RT were 1.81 (1.6-1.9) and 2.2 (2.1-2.4), 1.79 (1.5-1.9) and 2.1 (2.0-2.4) and 1.85 (1.6-2.2) and 2.2 (2.0-2.4) respectively, and were comparable. FeV1 and FVC remained within 80 to 120% of the baseline values in 37 pts (20 Arm A vs 17 Arm B, p = 0.5). FeV1 and FVC were reduced by more than 80% at 6 m in 3 pts of Arm A and 3 pts in Arm B (p = 0.7), while this was improved by over 120% in 5 pts (2 vs 3, p = 1). RT0 grade 2-3 radiation dermatitis was seen in 33 pts (15 vs 18, p = 0.55) while 5 pts had grade 4 toxicity (2 vs 3, p = 1). There was no treat-ment interruption because of toxicity.

**Table: 182P**

<table>
<thead>
<tr>
<th>Cosmetic Outcome</th>
<th>Mild change</th>
<th>Marked change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast Shrinkage</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Breast Hardness</td>
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<td>2</td>
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<tr>
<td>Breast Swelling</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Change in Skin appearance</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Self-breast assessment</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Photographic breast assessment</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>

**Overall:** 18 pts had excellent cosmesis (7 vs 11, p = 0.4) while 32 had good cosmesis. (18 vs 14, p = 0.4).

**Conclusions:** HFRT along-with concurrent Letrozole is well tolerated. However, pa- tients are being followed to assess loco-regional disease control and late toxicities. Legal entity responsible for the study: All India Institute of Medical Sciences

**Funding:** None

**Disclosure:** All authors have declared no conflicts of interest.

### 183P Intrinsically tumor features underlying clinical subtype discordance in early breast cancer

V. Kotoula 1, E. Giamoutsourou 1, K. Papadopoulou 1, I. Tikas 1, K. Manousou 1, M. Bobos 1, S. Tzikon 1, G. Lazaridis 1, I. Efstratiou 1, F. Zagoura 1, G. Pentheroudakis 1, H. Gogas 1, C. Christodoulou 1, A. Koutas 1, A. Pymyi 1, C. Papandreou 1, P. Papakosta 1, D. Bafaloukos 1, D. Pectasides 1, G. Fountzilas 1

1Data Office, Hellenic Cooperative Oncology Group (HeCOG), Athens, Greece, 2Computational Genomics Laboratory, Victor Chang Cardiac Research Institute, Darlinghurst, Australia, 3Department of Medical Oncology, University Hospital of Larissa, Larissa, Greece

**Background:** Despite efforts for laboratory and method harmonization, discordant clinical subtypes for ER/PgR/HER2 that determine treatment selection for breast cancer patients in clinical practice, still pose a challenge.

**Methods:** We investigated the clinical relevance of discordant clinical subtypes and their clinicopathological and genotype characteristics (60-gene panel) in a series of 1427 breast cancer patients treated within 4 adjuvant trials (2 in the pre- and 2 in the post-trastuzumab era, recruitment period 1997 – 2012). Treatment decisions were based on local laboratory typing; all patients were re-typed centrally. Disease-free sur- vival was assessed.

**Results:** We observed 340 (23.8%) discordant tumors for ER/PgR and/or HER2, rang- ing from 30% in the oldest to 19% in the most recent trial (p = 0.004); Cohen’s K was 0.512 for all subtypes, 0.538 for ER/PgR and 0.687 for HER2. ER/PgR discordance was associated with ER (p < 0.001) and PgR (p = 0.017) heterogeneity, basal phenotype, as well as higher grade, TILs and Ki67 labeling (all p < 0.001). HER2 discordant tumors had lower HER2 gene and CEN17 copies, and lower HER2/CEN17 ratios (all p < 0.001). Triple-positive tumors were rarely (0.5%) retyped as triple-negative (TN). ER/PgR discordant tumors had mutation patterns resembling HER2+ and TN, e.g., inversed TP53 and PIK3CA mutation prevalence (p < 0.001). Mutation clustering and phylogenetic analysis distinguished between concordant ER-/PgR-/HER2+ tumors (73% of all tumors) and all other subtypes, with strong associations between ER-/ PgR-/HER2+ and ER-/PgR-/HER2- (p < 0.001). More relapses were noticed in pa- tients with ER/PgR and HER2 negative-to-positive cases who did not receive hormono-therapy and trastuzumab (multivariate p = 0.048 and p = 0.016, respectively), but not in positive-to-negative cases.

**Conclusions:** Apart from technical considerations, clinical subtype discordance may reflect the genetic background of breast cancers, which appear to evolve by deviating from the ER+/PgR+/HER2+ status. Development and reporting of phenotypic surrogates
predictive of discordance is needed for increasing diagnostic accuracy and appropriate treatment selection. Legal entity responsible for the study: Hellenic Cooperative Oncology Group (HeCOG)

Funding: HeCOG

Disclosures: H. Gogas: Advisory or consultancy role: AstraZeneca, MSD, Novartis, Roche. C. Papadopoulou: Honoraria and/or Advisory Role: Astellas Pharmaceuticals, AstraZeneca, Janssen Pharmaceutical, Merck S.A., Roche (Hellas) S.A., Sanofi-Aventis, Pfizer Hellas S.A., Merck Sharp & Dohme. G. Fournel: Honoraria: AstraZeneca. Consulting or Advisory Role: Pfizer, Sanofi, Roche. Stock ownership (an immediate family member): Ariad. All other authors have declared no conflicts of interest.

Distribution of genomically defined recurrence risk in luminal A and B breast tumors defined by immunohistochemistry: A retrospective study in Spanish population

S. Perez Ramirez1, M. del Monte-Millan2, S. Lopez-Tarrueza1, I. Martinez-Rodas1, Y. Jerez1, F. Lobas-Sampaio2, V. Izaurralde Peros1, N. Martinez-Jahez1, J.A. Garca-Saeza1, F. Moreno-Antun3, P. Zamora Aurion1, M.A. Arroyo Yustos3, M.A. Lara Alvarez4, E.M. Cienfuegos5, I. Manso Gonzalez6, J.A. Guea Martinez2, J.C. Lara Sanchez5, I. Valencia Maganto1, M. Martin1, I. Jimenez1

1Medical Oncology, Hospital Universitario General Universitario Gregorio Maranon, Instituto de Investigación Sanitaria Gregorio Marañón (IISGM), Madrid, Spain, 2Medical Oncology, Hospital Universitario Fundación Jimenez Diaz, Madrid, Spain, 3Medical Oncology, Hospital Universitario Ramón y Cajal, Madrid, Spain, 4Medical Oncology, Hospital Universitario Círculo San Carlos, Madrid, Spain, 5Medical Oncology, Hospital Universitario La Paz, Madrid, Spain, 6Medical Oncology, Hospital Universitario Principe de Asturias, Madrid, Spain, 7Medical Oncology, Hospital Universitario Infanta Leonor, Madrid, Spain, 8Medical Oncology, Hospital Universitario 12 de Octubre, Madrid, Spain, 9Medical Oncology, Hospital Universitario Severo Ochoa, Madrid, Spain

Background: Semiclassification immunohistochemical (IHC) expression of progesterone receptor (PR) adds prognostic value to the current IHC-based luminal A (LA) definition, such that patients’ status of LA (Ki-67 < 14%) and PR > 20% tumors can be spared from adjuvant chemotherapy (CT). Oncotype DX® (O DX) and MammanPres® (MP) assays have been validated as predictors of CT benefit. This study assessed the distribution of recurrence risk in LA and LB breast tumors as defined by Ki67 and PR.

Methods: A retrospective analysis was performed in 889 T1-2, N0-Nmic, M0 tumors from the Spanish population. Of note about half of pts with LB tumors had low recurrence risk indicating minimal benefit from adjuvant CT.

Results: Median age 54 years (18-77). All pts had HER2 negative tumors. Median tumor size 15 mm (2-88). Three hundred (33.7%) tumors were classified as LA and 589 (66.3%) as LB. Grade 1 tumors were higher in LA (27%) than in LB (19%) pts (p < 0.001). CT was first recommended in 137 pts (45.7%) with LA vs. 361 pts (61.3%) with LB tumors. ODX was performed in 432 (48.6%) pts and MP in 457 (51.4%).

Conclusion: There is a wide distribution of recurrence risk results between LA and LB tumors defined by Ki67 and PR which confirms the important role of gene-expression assays in adjuvant decision making. Of note about half of pts with LB tumors had low recurrence risk indicating minimal benefit from adjuvant CT.

Table: 184P

<table>
<thead>
<tr>
<th>Recurrence Risk (%)</th>
<th>LA (n = 300)</th>
<th>LB (n = 589)</th>
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</thead>
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<tr>
<td>Low</td>
<td>71.4</td>
<td>46.2</td>
</tr>
<tr>
<td>Intermediate</td>
<td>25.7</td>
<td>44.2</td>
</tr>
<tr>
<td>High</td>
<td>2.9</td>
<td>9.6</td>
</tr>
<tr>
<td>MP (n = 457)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>81.2</td>
<td>54.2</td>
</tr>
<tr>
<td>High</td>
<td>18.8</td>
<td>45.8</td>
</tr>
</tbody>
</table>

Conclusions: There is a wide distribution of recurrence risk results between LA and LB tumors defined by Ki67 and PR which confirms the important role of gene-expression assays in adjuvant decision making. Of note about half of pts with LB tumors had low recurrence risk indicating minimal benefit from adjuvant CT.

Distribution of genomically defined recurrence risk in luminal A and B breast tumors defined by immunohistochemistry: A retrospective study in Spanish population

S. Perez Ramirez1, M. del Monte-Millan2, S. Lopez-Tarrueza1, I. Martinez-Rodas1, Y. Jerez1, F. Lobas-Sampaio2, V. Izaurralde Peros1, N. Martinez-Jahez1, J.A. Garca-Saeza1, F. Moreno-Antun3, P. Zamora Aurion1, M.A. Arroyo Yustos3, M.A. Lara Alvarez4, E.M. Cienfuegos5, I. Manso Gonzalez6, J.A. Guea Martinez2, J.C. Lara Sanchez5, I. Valencia Maganto1, M. Martin1, I. Jimenez1

1Medical Oncology, Hospital Universitario General Universitario Gregorio Maranon, Instituto de Investigación Sanitaria Gregorio Marañón (IISGM), Madrid, Spain, 2Medical Oncology, Hospital Universitario Fundación Jimenez Diaz, Madrid, Spain, 3Medical Oncology, Hospital Universitario Ramón y Cajal, Madrid, Spain, 4Medical Oncology, Hospital Universitario Círculo San Carlos, Madrid, Spain, 5Medical Oncology, Hospital Universitario La Paz, Madrid, Spain, 6Medical Oncology, Hospital Universitario Principe de Asturias, Madrid, Spain, 7Medical Oncology, Hospital Universitario Infanta Leonor, Madrid, Spain, 8Medical Oncology, Hospital Universitario 12 de Octubre, Madrid, Spain, 9Medical Oncology, Hospital Universitario Severo Ochoa, Madrid, Spain, 10Medical Oncology, Hospital Universitario de Fuenlabrada, Madrid, Spain, 11Medical Oncology, Hospital Universitario Fundación Alcorcón, Universidad Rey Juan Carlos, Madrid, Spain, 12Former Regional Oncology Coordinator, Ministry of Health, Madrid, Spain

Background: Semiclassification immunohistochemical (IHC) expression of progesterone receptor (PR) adds prognostic value to the current IHC-based luminal A (LA) definition, such that patients’ status of LA (Ki-67 < 14%) and PR > 20% tumors can be spared from adjuvant chemotherapy (CT). Oncotype DX® (ODX) and MammanPres® (MP) assays have been validated as predictors of CT benefit. This study assessed the distribution of recurrence risk in LA and LB breast tumors as defined by Ki67 and PR.

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Results: Median age 54 years (18-77). All pts had HER2 negative tumors. Median tumor size 15 mm (2-88). Three hundred (33.7%) tumors were classified as LA and 589 (66.3%) as LB. Grade 1 tumors were higher in LA (27%) than in LB (19%) pts (p < 0.001). CT was first recommended in 137 pts (45.7%) with LA vs. 361 pts (61.3%) with LB tumors. ODX was performed in 432 (48.6%) pts and MP in 457 (51.4%).

Conclusion: There is a wide distribution of recurrence risk results between LA and LB tumors defined by Ki67 and PR which confirms the important role of gene-expression assays in adjuvant decision making. Of note about half of pts with LB tumors had low recurrence risk indicating minimal benefit from adjuvant CT.
latter was approved for the risk of distant relapse estimation in postmenopausal women with hormone receptor (+), node (-) early stage breast cancer patients; and is a daily-used tool assessing the need of adjuvant chemotherapy.

Methods: The analyses were performed in paraffin embedded tissues (FFPE) from 96 patients recruited in a multicenter, prospective, non-randomized tri in negative breast cancer trial (NCT01560663). Pre-treatment core biopsies were performed following clinical practice guidelines and conserved as FFPE for further RNA extraction. PAM50 was performed on both NanoString nCounter® and RNA-Seq technologies. Subtype assignment was based on the nearest centroid similar following this procedure for both platforms.

Results: Subtype calling agreed on 96% of the cases (NanoString nCounter®/RNA-Seq discordances: 3 Basal-like/HER2-enriched and 1 HER2-enriched/LumA). Both the Spearman correlation to each of the centroids and the risk of recurrence (ROR) were discordances: 3 Basal-like/HER2-enriched and 1 HER2-enriched/LumA). Both the latter procedures provide similar results to the NanoString nCounter®, with the latter providing lower cost and more simplicity in its use.

Clinical trial identification: NCT01560663

Legal entity responsible for the study: Instituto de Investigación Sanitaria Gregorio Marañón (IDGM)

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Table: 187P

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<td>42%</td>
<td>40%</td>
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<td>67%</td>
<td>41%</td>
<td>3%</td>
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<td>44%</td>
<td>26%</td>
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<td>44%</td>
</tr>
</tbody>
</table>

a. Overall: any discordance in risk classification between the RS assay and other; 1-level: discordance of one risk category (low ← intermediate or intermediate ← high); 2-level: discordance of two risk categories (low ← high); b. Four studies lacked risk classification information appropriate for inclusion in this table. c. Study used nonstandard RS cutoffs for the RS vs. MMP comparison.
recommended for 101 patients (45.9%), the option of chemotherapy was discussed/ offered to 31 (14.1%) and 88 (40.0%) were not offered chemotherapy. Overall, 160 pa-
tients (25.9%) received chemotherapy. Where oncologists recommended chemotherapy to pa-
tients (n = 231), 59.7% of patients went on to receive chemotherapy. Where oncologists had offered or discussed chemotherapy as an option (n = 58), 27.6% of patients went on to receive it. The most common regimes were FEC75X6 (23.9%), ECAn (13.8%) and ECAn (9.4%), with 13.2% of patients receiving 1997 generation chemotherapy (FEC75/T, TC or E0/taxane); other regimes included ACx4, TCx4 and weekly paclitaxel.

Conclusions: Throughout the UK, about half of patients tested had low risk Oncotype scores and the majority (74.1%) of patients tested did not receive chemotherapy. The widest variation in clinical practice was observed in interpreting intermediate risk Oncotype results, and in the chemotherapy regimens offered.

Legal entity responsible for the study: Judy King

Funding: None

Disclosure: All authors have declared no conflicts of interest.

189P Enhancing decision-making about adjuvant chemotherapy in ER+, HER2- early breast cancer (EBC) following EndoPredict testing

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Background: Chemotherapy side-effects can be substantial. There is increasing recog-
nition that with surgery, radiotherapy and hormone treatment (tmt), many patients (pts) derive no benefit from chemotherapy and experience only iatrogenic harm. Gene expression profiling tests can help refine recurrence risk and likely chemotherapy bene-
fit. EndoPredict is a multigene test which includes clinical-pathologic parameters to produce an EPclin score classifying risks of distant recurrence as low or high for ER+ve HER2-ve pts treated with adjuvant endocrine tmt alone. We compared tmt decisions pre and post EndoPredict test results, pts’ anxiety, decisional conflict and oncologists’ confidence about decisions made.

Methods: 14 oncologists in 7 UK hospitals saw 149 pts judged to have equivocal indica-
tions for chemotherapy. Pts and oncologists discussed provisional tmt decisions based on usual prognostic factors. These decisions were reconsidered when EPclin results were available. Pre and post-test pts completed Spielberger’s State/Trait Anxiety inven-
tory (STAI) and a decision conflict scale (DCS). Oncologists additionally recorded basic clinical details, their agreement with, and confidence about tmt decisions (endo-
crine (E) therapy +/- chemotherapy (C)).

Results: 66.7% pts with an initial E alone decision and a high risk result upgraded to E+ C. 9.4% pts with initial E+C decisions and high risk results downgraded to E alone. None of 46 pts initially favouring E alone who were low risk changed decisions. 82.8% who initially wanted E+C and had low risk scores downgraded to E alone. Endopredict results increased oncologists’ confidence (8% ‘strongly agreed’ pre-test, 50% post-test). Oncologists neither agreeing nor disagreeing with decisions fell (24% to 5%). Anxiety was stable in pts with unchanged decisions. Pts whose tmt was downgraded had signifi-
cantly lower anxiety scores (p < 0.01). Those whose tmt was upgraded had increased scores (p < 0.001). Likewise overall uncertainty on DCS fell post-test (p < 0.023).

Conclusions: EndoPredict scores increased oncologists’ and pts’ decision-making confi-
dence, generally improved the matching of therapy decisions.

Clinical trial identification: ISRCTN69220108

Legal entity responsible for the study: David Bloomfield

Funding: Myriad Genetics

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190P Circulating ESR1 mutations at the end of aromatase inhibitor adjuvant treatment and after relapse in breast cancer patients

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Background: Detection of ESR1 circulating mutations is associated with acquired resis-
tance to aromatase inhibitor (AI) in metastatic breast cancer. Until now, the presence of ESR1 circulating mutations at the end of the adjuvant treatment by AI in early breast
cancer had never been clearly established. In this context, the aim of the present study was to evaluate the ESR1 circulating mutation frequency at the end of adjuvant treat-
ment in patients with a subsequent local or metastatic relapse.

Methods: This monocentric retrospective study was based on available stored plasma
data and included all early breast cancer patients who completed at least 2 years of AI adju-
vant treatment and experienced a documented relapse at least 6 months after the end of their treatment. ESR1 circulating mutations (D538G, Y537S/N/C) were detected by droplet digital PCR in plasma samples taken both at the end of adjuvant treatment and on AI progression in patients re-exposed to AI during the metastatic phase.

Results: A total of 39 patients were included, with a median adjuvant AI exposure of 60 months (range 41–85). One patient (2.6%) had a local relapse only, while all the others (97.4%) had a metastatic relapse during follow-up. Median delay between the end of the adjuvant treatment and relapse was 25 months (range 6-71). No ESR1 circulating mu-
tation was detectable at the end of AI adjuvant therapy. In contrast, among the 25 pa-
tients (64%) who progressed on AI during the metastatic setting, 17 plasma samples were available and 7 patients (41.2%) had a detectable mutation.

Conclusions: Our results highlighted that there is no emergence of circulating ESR1 mutation at the end of an AI-based adjuvant treatment in hormone receptor positive breast cancer patients. In contrast, and as expected, we showed that re-exposure to AI in the metastatic setting induced circulating mutation detection in a significant fraction of the patients. Our present findings point out the low interest in ESR1 circulating mu-
tation detection during the adjuvant setting, even for patients that will relapse.

Legal entity responsible for the study: Centre Henri Becquerel

Funding: None

Disclosure: All authors have declared no conflicts of interest.

191P Pathological proliferation score to predict genomic risk categories in early stage breast cancer

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Background: Five of the 16 cancer-related genes used to calculate the Recurrence Score (RS) are proliferative genes. Appropriate utilization of an expensive test is important especially in areas of limited resources. A relatively inexpensive ‘Pathological Proliferative score’ (PPS) of a tumor may help group patients in risk categories correlat-
ing with the RS.

Methods: We retrospectively studied 205 patients with Lymph node negative, hormone receptor (HR) positive, HER2 negative status (ODX candidates) between 1990-2015 treated across three rural community oncology practices. Proliferation score was calculated by com-
bining tumor grade, visual mitotic score and Ki67 immunostaining (on a scale of 1-3, lowest score of 1, highest score of 3). Log-rank test was used for survival analysis.

Results: PPS correlated with ODX risk recurrence (p < 0.001, Fischer’s Exact test) [Table]. PPS predicted FFP (p = 0.014) at 10 years with Prs (3-4) 96.2%±2.5%, Prs (5-7) 91.6±5.2% and Prs > (7-9) 75±6.1%. It did not predict FFP (p = 0.77), OS (p = 0.84). Type of adjuvant treatment or none did not affect Low Prs (3-4) 10 yr FPP (p = 0.18 and OS (p = 0.33). Int/High Prs (5-9) showed benefit with adjuvant hormonal therapy compared to none at 10-year OS (p < 0.001), FPP (p = 0.002) and FFP (p = 0.003).

Table: 191P Correlation of ODX with PrS

<table>
<thead>
<tr>
<th>Proliferative Score (n = 190)</th>
<th>Genomic Risk</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 – 4</td>
<td>Low</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5 – 6</td>
<td>Intermediate</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>7 – 9</td>
<td>High</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(n = 119)</td>
<td>0 (58%)</td>
<td>(n = 137)</td>
</tr>
<tr>
<td>(n = 37)</td>
<td>6 (13%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>(n = 40)</td>
<td>0 (0%)</td>
<td>15 (64%)</td>
</tr>
</tbody>
</table>

*P-value based on Fisher’s Exact test
The 10 yr OS (p < 0.75), PFS (p < 0.76) and FFP (p = 0.88) was not influenced by addition of adjuvant chemotherapy.

Conclusions: Pr5 which may represent an inexpensive screening approach to identify patients with a low ODX RS that have excellent outcomes despite the type of adjuvant treatment. ODX testing is unlikely to re-categorize them. Higher (5-9) Pr5 was not predictive of chemotherapy benefit, unlike high ODX. Lack of standardization of Ki67 staining, retrospective nature of the study while important should be tested in an expanded and prospective setting.

Legal entity responsible for the study: Kymera Independent Physicians

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Population sizes of patients (pts) with node negative (N0), HR+, HER2− primary breast cancer (BC), using standard and TAILORx 21-gene recurrence score (RS) cut-off values (COV)

<table>
<thead>
<tr>
<th>RS group</th>
<th>US (N = 513035)</th>
<th>UK (N = 10154)</th>
<th>Germany (N = 14856)</th>
<th>France (N = 4238)</th>
<th>RoW (N = 66964)</th>
<th>All regions (N = 609247)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤11</td>
<td>109396</td>
<td>21</td>
<td>1775</td>
<td>17</td>
<td>2714</td>
<td>18</td>
</tr>
<tr>
<td>11-17</td>
<td>178070</td>
<td>35</td>
<td>3171</td>
<td>31</td>
<td>5295</td>
<td>36</td>
</tr>
<tr>
<td>18-25</td>
<td>135783</td>
<td>26</td>
<td>2844</td>
<td>28</td>
<td>4207</td>
<td>28</td>
</tr>
<tr>
<td>26-30</td>
<td>35512</td>
<td>7</td>
<td>848</td>
<td>8</td>
<td>1161</td>
<td>8</td>
</tr>
<tr>
<td>≥31</td>
<td>54274</td>
<td>11</td>
<td>1516</td>
<td>15</td>
<td>1479</td>
<td>10</td>
</tr>
</tbody>
</table>

Legal entity responsible for the study: Jens-Uwe Blohmmer

Funding: Genomic Health

The 70-gene signature in node positive breast cancer: 10-year follow-up of the observational RASTER study


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Background: In early stage breast cancer patients, with axillary lymph node metastasis, the 70-gene signature, MammaPrint® (MP) identifies patients with a High or Low Risk of distant breast cancer (BC) recurrence. For MP Low Risk (G genieomic-low) in patients with up to 3 positive lymph nodes (N1-3), the MINDACT trial (Cardoso, NEJM 2016) showed that it might be safe to forgo adjuvant chemotherapy. Here we evaluated MP expression data to identify patients with high expression of estrogen response genes, a potential marker for increased risk of late recurrence.

Methods: The estrogen receptor (ER) gene expression data was obtained from the Molecular Signatures Database. Within each group, associations with event-free survival (EFS) as determined by univariate Cox regression were calculated. The top 71 estrogen response genes were ranked on their association with EFS as determined by multivariate Cox regression. The 4 Hallmarks of breast cancer were defined as a potential marker for increased risk of late recurrence. The biological meaning of these Hallmarks is increased expression of estrogen response genes, which is associated with a greater risk for late recurrence in patients with ER+/HER2 breast cancer.

Results: In patients with ER+ breast cancer, 50% of recurrences occur > 5 years after diagnosis (i.e. late recurrence). Clinical trials report contradicting results on the effect of extended endocrine therapy > 5 years to reduce late recurrence risk. Using publicly available breast cancer gene expression data, we aimed to gain insight into the biology that increases the risk for late recurrences.

Methods: Gene expression profiles of primary ER+/HER2 breast cancer patients were collected with disease-free survival (DFS) data, defined as time of diagnosis to local recurrence or distant metastasis. We defined (i) a group containing all patients (n = 2,231), (ii) a group that received 5 years of endocrine therapy only (n = 591), and (iii) a group that received no systemic therapy (n = 497). For each group, genes were ranked on their association with DFS as determined by multivariate Cox regression with age, tumor size, grade, lymph node status, and therapy as covariates. Gene set enrichment analysis (GSEA) was performed on these gene lists with the Hallmark collection from the Molecular Signatures Database. Within each group, associations with early recurrence were studied in all patients with censoring at 5 years if no event occurred < 5 years after diagnosis (set I). To study associations with late recurrence, a second set was defined that contained only patients with a follow-up ≥ 5 years and no event < 5 years after diagnosis (set II).

Results: Within all patients and the group that received 5 years of endocrine treatment only, higher expression of genes belonging to the Hallmark ‘estrogen response late’ was associated with longer DFS in set I and shorter DFS in set II. This Hallmark contains estrogen-responsive genes identified in estrogen receptor+ breast cancer cell lines. However, in patients who received no systemic treatment, higher expression of these genes was associated with shorter DFS in both set I and II. The biological meaning of these Hallmarks is increased expression of estrogen response genes, which is associated with a greater risk for late recurrence in patients with ER+/HER2 breast cancer. Potentially, patients with ER+ tumors with high expression of these genes might benefit most from extended endocrine therapy.

Legal entity responsible for the study: R.S.N. Fehmann

Funding: Dutch Cancer Society grants RUG 2010-4739 and RUG 2013-5960, NWO-Veni grant (916-10025) and a Mandema Stipendium.

Disclosure: All authors have declared no conflicts of interest.

Comparisons of tumor-infiltrating lymphocytes and 21-gene recurrence score in ER-positive/HER2-negative breast cancer

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Background: Recent meta-analysis showed that tumors with high tumor-infiltrating lymphocytes (TIL) have a higher probability of pathologic complete response even in luminal/HER2-negative breast cancer. Also, the 21-gene recurrence score (RS) predicts the clinical benefit of chemotherapy for ER-positive/HER2-negative women. We compared two markers in those cancer.

Methods: In ER-positive/HER2-negative patients treated with primary surgery, the RS (OncoType DX® Breast Cancer Assay, Genomic Health, Inc., USA) was obtained. We evaluated TIL in H&E slides of surgical specimens by standardized methodology proposed by the international TIL-working group. In 198 women, the percentage of stromal TIL was successfully assessed. In accordance with the recent meta-analysis, the degree of TILs were categorized as high (> 60%), intermediate (11-59%), and low (< 10%).

Results: Ninety-seven (49.0%), 88 (44.4%), and 13 (6.6%) had low, intermediate, and high TILs, respectively. There is a significant but weak correlation between continuous RS and continuous TIL (Pearson’s R = 0.201, P = 0.004).

Conclusions: We found tumors with high TIL tend to have a higher RS in ER-positive/HER2-negative breast cancer. We also noted that the rate of high-TIL tumors is higher in the intermediate RS or the high RS (1.0% for low RS tumors, 12.5% for intermediate RS tumors, and 13.6% for high RS tumors; P = 0.007).

Table 1: 194P

<table>
<thead>
<tr>
<th>Low or Intermediate RS</th>
<th>High RS</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low RS (N = 98)</td>
<td>97 (99%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Intermediate RS (N = 80)</td>
<td>70 (88%)</td>
<td>10 (12%)</td>
</tr>
<tr>
<td>High RS (N = 20)</td>
<td>18 (90%)</td>
<td>2 (10%)</td>
</tr>
</tbody>
</table>

Legal entity responsible for the study: N/A

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Disclosure: All authors have declared no conflicts of interest.

Understanding BRCA1 and BRCA2 mutated breast cancer cases in Romania: First report on founder mutations in Romanians

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Background: First systematic analysis of BRCA1 (B1) or BRCA2 (B2) mutations in high-risk Romanian breast cancer patients (pts) aiming at defining founder mutations.
Methods: This prospective study evaluated the germline B1/B2 mutations in 250 high-risk breast cancer pts tested between 02.2015-12.2016 at IOCN. Inclusion criteria selected pts diagnosed with triple negative breast cancer under the age of 50, or having conventional family history criteria. All pts signed an informed consent. B1/B2 testing was performed using an Amplicon-based sequencing analysis, on the Ion Torrent Personal Genome Machine at RCFG. Pathogenic mutations were validated using Sanger technology. MLPFA was performed for all pts.

Results: Of the 250 pts with breast cancer, 44 (17.6%) carried pathogenic mutations, 29 pts (11.6%) in B1 and 35 (14%) in B2, while 18 patients (7.2%) carried a Variant of Uncertain Significance (VUS). Patient features analysis confirmed the prevalence of younger age, higher grade, hormone receptor negative and Her2 negative status among mutated patients (data not shown). Out of the 16 distinct deleterious mutations identified, 7 (43.75%) occurred in B1 and 9 (56.25%) in B2. The founder mutations identified in B1 gene were: c.3329_3330delG (5.626delGp) 11 pts (37.9%), c.4607_C>T 9 pts (31.03%) and c.1187_1188insG 4 pts (13.79%). Other B1 mutations where: c.1687C>T, c.941delG (6.89%), and c.2416delG (3.44%), c.121+2T (3.44%), c.6894delAG (3.44%) in one patient respectively. For B2 gene, c.9371A>T (46.66%) was identified as founder mutation (7 pts, 46.66%). Other mutations were found each in one patient (6.66%): c.1528G>C, c.4022G>C, c.7007C>A, c.8695C>T, c.2953delA, c.8608C>T, c.8755_1G>A, c.8695C>T. Of the founder mutations identified, two (c.3607C>T and c.9371A>T) have not been previously identified as founder mutations in any Eastern European country.

Conclusions: This prospective study presents the first extensive results of germline B1/B2 mutations in Romanian high-risk breast cancer pts. Our results indicate that at least four recurrent (B1/B2) mutations qualify as founder mutations; two being newly identified as carrying a founder effect. ClinicalTrials.gov identifer: NCT02317120.

Clinical trial identification: NCT02317120

Legal entity responsible for the study: Alexandre Eniu

Funding: A Eniu.

Research support: AstraZeneca, Roche, Novartis, Celltrion. All other authors have declared no conflicts of interest.

199P The prevalence of CD146 expression in breast cancer subtypes and its relation to outcome

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Background: CD146 has several putative (patho)physiological roles in breast cancer. The most prominent is its involvement in the induction of epithelial-to-mesenchymal transition, which might have an effect on cancer phenotype and aggressiveness. Here, we investigated the prevalence of CD146 expression and its prognostic role in breast cancer subtypes.

Methods: In total, 1,025 breast cancer patients were available for this retrospective study. From all patients, formalin-fixed paraffin-embedded primary breast cancer tissue was collected and embedded in tissue microarrays, which were stained for CD146. CD146 expression was defined as ? 1% of the tumor cells showing CD146 membrane staining. Clinical data were available from all patients (median follow up 118 months, range 4-120). For subtype analysis the Pearson chi-square test was used and the Cox proportional hazards model for survival analyses. Only patients who were lymph node negative and did not receive (neo)adjuvant systemic treatment were included in the survival analyses (n = 551).

Results: 113 (11%) out of 1,025 tumors showed CD146 expression. Of these, 43% of the tumors had > 50% of the tumor cells showing CD146 membrane staining. From the molecular subtypes, CD146 positive tumors are often of the triple negative subtype (76 out of 119 (64%), p = 0.001) and histologically of the medullary type (11 out of 23 (48%), p <0.001). In univariable analysis, CD146 was a prognostic factor for both poor metastasis-free survival (MFS) and overall survival (OS) (respectively HR 1.65, 95% CI 1.02-2.66, p = 0.041 and HR 1.66, 95% CI 1.03-2.69, p = 0.037). When correcting for the traditional prognostic factors (including age, tumor size and grade, ER, PR and HER2) in multivariable analysis, CD146 was not an independent prognostic factor for MFS and OS (respectively HR 1.63, 95% CI 0.93-2.87, p = 0.088 and HR 1.48, 95% CI 0.82-2.61, p = 0.197).

Conclusions: CD146 protein expression is present in 11% of the primary breast cancer tumors and is most prevalent in the triple negative and medullary subtypes. CD146 is a prognostic factor for MFS and OS in breast cancer patients, but it is not independent of the traditional prognostic factors. Its potential impact on outcome to systemic treatment such as endocrine therapy, remains to be established.

Legal entity responsible for the study: Erasmus University Medical Center

Funding: None

Disclosure: All authors have declared no conflicts of interest.

200P Vitamin D as a prognostic factor in triple negative early breast cancer

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Background: Triple negative breast cancer remains without a target therapy. Interventions that could improve pathological complete response (pCR) rates are required. Metabolism of vitamin D could be involved in chemotherapy response.

Methods: A series of 147 patients with early or locally advanced triple negative breast cancers was retrospectively analyzed from 2007 to 2016. Patients from 2015 to 2016 period were supplemented with vitamin D and calcium (880UI/1000mg). Analysis of clinicopathological, immune variables and vitamin D pathway were correlated to pCR.

Results: Median age was 53, median tumor size 30mm, 48% had nodal involvement, and median ki67 expression was of 70%. Androgen receptor was expressed in 28% of tumors analyzed, EGFR in 89%, CK5/6 in 63%. Mean stromal T lymphocytes infiltrates (STILs) was of 28%, mean PD-L1 expression of 128, mean M3HP1 expression of 125, and mean VDRnuc expression of 132. pCR rate was of 40%, and with patients with vitamin D supplementation was 64% (16/25). Only VDRnuc expression was associated with pCR (p = 0.047) in the univariate and multivariate analysis. Patients with high expression of VDRnuc in tumor had no evidence of relapse (p = 0.024), with similar curves than those who achieve pCR (p = 0.000).

Conclusions: VDRnuc expression is a strong predictive (p = 0.047 with pCR) and prognostic (p = 0.024 with relapse) in triple negative breast cancer. Role of supplementation needs to be tested if it could improve VDRnuc levels, whereas in our series patients with supplementation had better pCR rates.

Legal entity responsible for the study: Hospital Universitari Arnu Anna de Vilanova de Lleida Instituto de Recerca Biomèdica

Funding: None

Disclosure: All authors have declared no conflicts of interest.
CDK12: New breast and ovarian cancer predisposition gene in Tatar population?

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Background: The development of hereditary ovarian and breast cancer (OC/BC) is often caused by genetic defects in the DNA repair system. However, the diagnoses in most medical centers of Russia includes PCR-based identification only the eight common mutations in BRCA1/2 for the Slavic population. Previously we established that patients of the Tatar population with OC/BC did not possess most of Slavic mutation and a significant part of the predisposition is due to other mutations in the genes of the homologous recombination (HR) system. The aim of this work is the analysis of the germline mutations in the HR genes.

Methods: The DNA from 175 blood samples from patients of the Volga District were analyzed by targeted NGS (Roche NimbleGen, Illumina MiSeq), the comparison groups included blood samples from patients of Slavic origin.

Results: 62% of the detected pathogenic mutations were presented in the BRCA1/2 genes. The remaining mutations were found in other genes of the repair system (HMGD Professional 2017.1 database). An unexpected finding was the detection of a germline splicing mutation c.1047-2A>G in CDK12 gene (Chr17:GRCh37:37627130A>G, NM_006569.3) in patients of Tatar origin (Table1). Mutation c.1047-2A>G is more common in patients with OC/BC in comparison with healthy controls (7/224 vs 0/316, p = 0.002, OR = 21.49, CI95% = 1.23–377.25).

Conclusions: Gene CDK12 is one of the most frequently altered genes in serous ovarian carcinomas, but significance of CDK12 germline mutations in hereditary cancers remains be defined. Its role in carcinogenesis of OC was established recently and CDK12 was not included in most NGS panels of HR genes. Our study demonstrates that CDK12 may be novel candidate gene for OC/BC genetic predisposition. Notably, frequency of CDK12 c.1047-2A>G (6.4%) mutation is comparable with frequency of founder-mutation BRCA1 5382insC (7.4%), that indicates its possible founder role in Tatar population.

Legal entity responsible for the study: Tatarstan Cancer Center

Funding: Kazan (Volga Region) Federal University, Tatarstan Cancer Center

Disclosure: All authors have declared no conflicts of interest.

Prognostic value of master transcriptional regulators (MTRs) in early stage breast cancer

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Background: Multigene prognostic signatures (MGPS) enable identification of candidate patients (pts) for treatment de-escalation in early stage BC. However, currently available MGPS do not completely address clinical needs by adequately incorporating lymph node (LN)–positive pts and clinicopathological information (CPI). Here, we present OncoMasTR, a MGPS for determining the risk of distant recurrence (DR) in ER-positive, HER2-negative BC pts with up to 3 involved LNs. OncoMasTR, discovered via a novel network analysis methodology that determines upstream MTRs has been mechanistically verified and offers improved prognostic value compared to existing MGPS. OncoMasTR has been further trained to include LN–positive pts and CPI.

Methods: Two independent sample sets: 225 pts from Malmo University Hospital and 106 pts from Skane University Hospital were used for training, cross-validation and refinement of OncoMasTR. RNA extracted from 225 archived tissues was analysed by RT-qPCR and expression levels of the MTRs were determined by normalising against the expression levels of reference genes. The strongest prognostic combinations of MTRs were identified using statistical models of all possible combinations of MTRs. Clinical performance of the models with the best cross-validated performance in the training data were further evaluated in the 106 independent samples.

Results: OncoMasTR classifies up to 72% of LN0 pts and 60% of LN1-3 pts as low risk, with only 4.9% and 5.5% recurrence rate within the respective groups. When incorporating selected CPI, its prognostic performance further improved to a concordance index of above 0.8. Results showed that the OncoMasTR Molecular score (mS) alone adds statistically significant information to the CPI, and the Combined score (CS) also added for breast carcinomas at a UK specialist cancer centre over a 10 year period (2004–2014)

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Background: Carcinosarcoma of the breast is a rare and aggressive type of breast cancer presenting as a high grade tumour with lower rates of both lymph node metastasis and oestrogen and progesterone receptor (ER/PR) expression when compared to the more common types of breast cancer, carrying a less favourable prognosis. We present the clinical and pathological findings and outcomes of a series of patients diagnosed and treated for breast carcinosarcoma at a UK specialist cancer centre.

Methods: We conducted a retrospective review of data for all patients diagnosed with breast carcinosarcoma between October 2004 and October 2014 at the Clatterbridge Cancer Centre NHS Foundation Trust.

Results: Nine patients were diagnosed in the 10-year period, with a median age at diagnosis of 73 years (range 37–96 years). Seven patients (77%) were postmenopausal. Six patients (66.7%) presented with a palpable mass. T1, T2, and T3 were found in 1, 6 and 2 patients respectively. N0, N1, and N2 were found in 6, 2 and 1 patients respectively. All other authors have declared no conflicts of interest.
Background: The biological drivers of prognosis for pure ILC are not entirely clear. The aim of this analysis was to investigate the molecular and immune-related portrait of prognostic outliers to identify different patterns of expression associated with prognosis and potentially druggable.

Methods: Clinical-pathological multi-center data of resected early-stage pure ILC patients was collected. Prognostic patterns were identified using multivariate hazard ratios, in order to derive a 3-class model (Poor/Intermediate/Good Prognosis). IHC (for Ph-mTOR, CDK6, PD-L1), FISH (for ER1, Ph-mTOR, CDK6, PD-L1) and H&E evaluation (stromal Tumor Infiltrating Lymphocytes, sTILs) were performed upon pts at Poor and Good Prognosis. Odds Ratios (OR) with 95% CIs for the risk of association with prognostic class of biomarkers was determined.

Results: Data from 457 pts were gathered (median age 57 years, median follow-up 75 months). The 3-class cross-validated model significantly differentiated DFS and OS (p < 0.0001, prognostic accuracy: 0.65 and 0.71, respectively). Based on DFS, 134 and 20 pts with Good and Poor prognosis, respectively, were identified. The preliminary and exploratory analysis of the first 64 pts (Good/Poor 14/20) is reported (OR < 1, higher chance to be associated with Good prognosis; OR > 1 higher chance to be associated with Poor prognosis).

Table: 204P

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Method</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>High sTILs</td>
<td>H&amp;E</td>
<td>0.22</td>
<td>0.01-5.8</td>
</tr>
<tr>
<td>Ph-mTOR deletion</td>
<td>FISH</td>
<td>0.33</td>
<td>0.17-0.69</td>
</tr>
<tr>
<td>ER1 gain</td>
<td>FISH</td>
<td>0.32</td>
<td>0.09-1.49</td>
</tr>
<tr>
<td>PD-L1 positive (IHC)</td>
<td>0.67</td>
<td>0.39-1.14</td>
<td></td>
</tr>
<tr>
<td>CDK4 deletion</td>
<td>FISH</td>
<td>1.22</td>
<td>0.31-5.15</td>
</tr>
<tr>
<td>PD-L1 deletion</td>
<td>1.25</td>
<td>0.92-1.72</td>
<td></td>
</tr>
<tr>
<td>Score 3+</td>
<td>CDK6</td>
<td>2.29</td>
<td>0.21-24.68</td>
</tr>
<tr>
<td>Score 3+</td>
<td>Ph-mTOR</td>
<td>2.48</td>
<td>1.61-10.05</td>
</tr>
<tr>
<td>ER1 deletion</td>
<td>FISH</td>
<td>2.75</td>
<td>0.23-23.04</td>
</tr>
<tr>
<td>CDK4 gain</td>
<td>3.18</td>
<td>0.15-66.36</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: Despite unpowered, these preliminary data suggest that Poor and Good prognosis are potentially associated to differential expression of a cluster of biomarkers: ER1 deletion, CDK4 gain, CDK6 and Ph-mTOR over-expression versus high sTILs, PD-L1 positive, ER1 gain and Ph-mTOR deletion, respectively.

Legal entity responsible for the study: University of Verona

Funding: None

Disclosure: All authors have declared no conflicts of interest.

205P The pregnancy and fertility (PREFER) study: A prospective cohort study on fertility preservation (FP) strategies in young early breast cancer (EBC) patients (pts)

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Background: Premature ovarian failure and subsequent infertility are possible long-term side effects of chemotherapy (CT) in young EBC pts. Limited data are available on the number of pts who consider FP strategies and on the reasons for refusal of these procedures. To address the significant challenges related to fertility issues, the PREFER study was developed as a national comprehensive program aiming to optimize care and improve knowledge around this topic.

Methods: This is a prospective cohort study ongoing across several Italian centers affiliated to the GIM (Gruppo Italiani Mammologa) study group. Oncologists offer the available FP strategies to young EBC pts undergoing (neo)adjuvant CT: oocyte cryopreservation (OC), ovarian tissue cryopreservation (OTC) and LHRH analogue (LHRHa) during CT. Eligible pts are premenopausal, ≤ 45 years, previously exposed to CT and/or radiotherapy. Primary objective is to obtain data about preferences and choices of young EBC pts on the FP strategies. Secondary objectives are to evaluate the success and safety of FP strategies, hormonal changes during CT and its impact on outcomes. The present analysis reports preliminary results of the study including pts enrolled at the coordinating center from November 2012 to May 2017.

Results: A total of 131 EBC pts were enrolled; median age was 38 years (24-45 34). Nine pts (6.87%) refused all FP options. Reasons for refusal were no interest in fertility preservation (5 pts), previous pregnancy (3 pts), no interest in having children (1 pt). LHRHa was accepted by 120 pts (91.6%) and 27 pts (20.6%) accepted gynecologic counseling. Among these pts, 10 (7.6%) accepted OC or OTC. Main reason for refusal of cryopreservation procedures was fear of delaying cancer treatment (3 pts). No complications were observed among women who underwent OC or OTC. Median number of mature oocytes yielded and cryopreserved was 8 (5-13). A patient had a spontaneous pregnancy following adjuvant treatment.

Conclusions: Despite the great importance of fertility issues in young EBC pts, a minority of them (7.6%) require to access cryopreservation procedures. This is crucial information from a public health perspective and for resource allocation.

Clinical trial identification: NCT02895165

Legal entity responsible for the study: IRCCS AOU San Martino IST, Genoa Italy

Funding: AIRC - Associazione Italiana per la Ricerca sul Cancro (IG 2013 No14272).

Disclosure: All authors have declared no conflicts of interest.
Background: In ABCSG-34, patients with HER2-negative breast cancer were randomized to preoperative standard of care therapy (SoC) with or without L-BLP25 (Stimuvax®). This report describes the quality-of-life (QoL) results of the trial.

Methods: 400 patients were randomized to receive SoC with or without L-BLP25. Postmenopausal women with low-risk disease (ER+/<10%, Ki67<14%, G2) received 6 months of letrozole; premenopausal and postmenopausal patients with triple-negative, ER-/<10%, Ki67 ≥14%, or G3 tumors received 4 cycles of epirubicin/ cyclophosphamide plus 4 cycles of docetaxel with or without L-BLP25. Primary end point results RCB and PCI rates were presented previously (SABCs 2016; Abstract Nr 850339). QoL was assessed with the EORTC QLQ-C30 and EORTC QLQ BR23 at baseline, before surgery, and up to 4 weeks thereafter. The objective was to evaluate differences of QoL in women treated with or without L-BLP25, as well as between the two regimens.

Results: 385 patients from 17 centers were included in the QoL analysis. There were no differences in QoL between patients receiving SoC only and those receiving additional L-BLP25. Impact on QoL was determined by the SoC therapy and by the timepoint of the assessment. Before surgery and 4 weeks thereafter patients receiving chemotherapy ± TL-BLP25 showed more improvement in the QoL scales role and social functioning, financial problems and body image than the patients receiving endocrine therapy ± TL-BLP25. Fatigue and hair loss were significantly more common in the chemotherapy arm than in the endocrine arm. At the time of surgery and thereafter, patients in both SoC arms had significantly negatively impacted QoL (physical, role, emotional, cognitive, social, sexual functioning, body image domains) as well as more fatigue, pain, dyspnea, breast and arm symptoms. There were no differences in global health status between the arms at the different time points.

Conclusions: Addition of L-BLP25 (Stimuvax) to SoC in HER2-negative EBC patients does not impair QoL.
DbPET was superior to detect residual primary tumors, especially noninvasive carcinoma, after NAC than WBPET. TNR was expected as the better parameter compared with WBPET-SUV in predicting the presence of residual primary tumors after NAC, compared with whole-body PET (WBPET).

Methods: Forty-five patients (47 tumors) underwent WB-PET and ring-type DbPET after NAC, and tumors were completely resected between January 2016 and March 2017. The pathological response was classified as complete remission (ypT0), residual intraductal disease (ypTis), or residual invasive disease (ypT>1). Standardized uptake value (SUV) and tumor-to-normal tissue ratio (TNR) were assessed.

Results: Twelve patients achieved ypT0 and 5 developed ypTis. DbPET detected all cases of ypTis and ypT0, detected only one case of ypT1. The specificity, sensitivity, and accuracy of WB-PET for ypT>1 were 54.3%, 83.3%, and 61.7%, respectively, and those of DbPET were 77.1%, 83.3%, and 78.7%, respectively. In the ypT0/ypTis/ypT>1 groups, the median WB-PET-SUV, DbPET-SUV, and DbPET-TNR were 1.00 (0.94–1.01), 1.71 (1.12–2.12) and 1.00 (0.91–1.01), respectively.

Conclusions: DbPET was superior to detect residual primary tumors, especially noninvasive carcinoma, after NAC than WB-PET. TNR was expected as the better parameter of pathological evaluation than SUV.

Legal entity responsible for the study: ABCSG

Funding: This study was supported by ABCSG. ABCSG was the regulatory sponsor of this trial. Merck provided financial funding and the study drug (IMP). This study was designed and conducted by ABCSG. Merck was not involved in collection, management, analysis, and interpretation of the data. ABCSG prepared and approved the manuscript. All co-authors have decided to submit the manuscript for publication.

Trial. Merck KGaA provided financial funding and the study drug (IMP). The study was designed and conducted by ABCSG. Merck was not involved in collection, management, analysis, and interpretation of the data. ABCSG prepared and approved the manuscript. All co-authors have decided to submit the manuscript for publication.

Background: Diagnostic methods to evaluate the response to breast cancer neoadjuvant chemotherapy (NAC) have been established. Dedicated breast PET (DbPET) is a high-resolution molecular breast imaging method, and we investigated the ability of DbPET to predict the presence of residual primary tumors after NAC, compared with whole-body PET (WB-PET).

Methods: Forty-five patients (47 tumors) underwent WB-PET and ring-type DbPET after NAC, and tumors were completely resected between January 2016 and March 2017. The pathological response was classified as complete remission (ypT0), residual intraductal disease (ypTis), or residual invasive disease (ypT>1). Standardized uptake value (SUV) and tumor-to-normal tissue ratio (TNR) were assessed.

Results: Twelve patients achieved ypT0 and 5 developed ypTis. DbPET detected all cases of ypTis and ypT0, detected only one case of ypT1. The specificity, sensitivity, and accuracy of WB-PET for ypT>1 were 54.3%, 83.3%, and 61.7%, respectively, and those of DbPET were 77.1%, 83.3%, and 78.7%, respectively. In the ypT0/ypTis/ypT>1 groups, the median WB-PET-SUV, DbPET-SUV, and DbPET-TNR were 1.00 (0.94–1.01), 1.71 (1.12–2.12) and 1.00 (0.91–1.01), respectively.

Conclusions: DbPET was superior to detect residual primary tumors, especially noninvasive carcinoma, after NAC than WB-PET. TNR was expected as the better parameter of pathological evaluation than SUV.

Legal entity responsible for the study: ABCSG

Funding: This study was supported by ABCSG. ABCSG was the regulatory sponsor of this trial. Merck KGaA, Darmstadt, Germany, 2Breast Surgery, Hiroshima University Hospital, Hiroshima, Japan, 3Breast Surgery, Hiroshima University Hospital, Hiroshima, Japan, 4Biostatistics, F. Hoffmann-La Roche Ltd., Basel, Switzerland, 5Global Oncology Product Development, F. Hoffmann-La Roche AG, Weihenstephan Garden City, UK, 6Global Development, Genentech, South San Francisco, CA, USA

Background: Atezo is an anti–programmed death–ligand 1 (PD-L1) monoclonal antibody that prevents PD-L1 from binding to PD-1 and B7.1 receptors, thereby restoring tumor-specific immunity. TNBC is characterized by PD-L1 expression on tumor-infiltrating immune cells (IC), a high mutation rate and high levels of tumor-infiltrating lymphocytes (TILs), suggesting a therapeutic opportunity for atezol. Atezo alone and in combination with nab-paclitaxel is well tolerated, with promising activity in metastatic TNBC, supporting its investigation in early-stage disease. IMpassion031, a global Phase III, double-blind, randomized, multicenter, placebo-controlled study, is being conducted to evaluate the efficacy and safety of neoadjuvant treatment with nab-paclitaxel + docetaxel in patients with all stages of TNBC. This choice and sequence of chemotherapy is selected to maximize the opportunity to establish a robust immune response.

Trial design: Patients (pts) with previously untreated, central laboratory–confirmed invasive TNBC with primary tumor size >2 cm and ECOG PS 0-1 are eligible. Exclusion criteria include history of invasive BC, stage IV disease, and prior immunotherapy or autoimmune disease. Approximately 204 pts will be randomized 1:1 to receive atezo (840 mg q2w) or placebo with nab-paclitaxel (125 mg/m² qw) for 12 weeks, followed by atezo (840 mg q2w) or placebo with docetaxel (60 mg/m² qw) + cyclophosphamide (600 mg/m² qw) for 4 cycles before surgery. Pts will be unblinded post-surgery and pts in the atezo arm will continue to receive atezo (1200 mg q2w × 11 doses). Stratification factors include stage II or III at diagnosis and PD-L1 expression (IC3 or IC1/2/3). The primary endpoint is pathological CR (pCR); key secondary endpoints include pT0 according to PD-L1 status, pT0 outcomes, event-free survival and overall survival. Tumor samples will be taken at baseline, on treatment (optional), at surgery and post-recurrence and will be assessed for biomarkers associated with responses and immune escape.

Clinical trial identification: NCT number available on poster

Legal entity responsible for the study: F. Hoffmann-La Roche Ltd.

Funding: F. Hoffmann-La Roche Ltd.

Disclosure: E.A. Mittendorf: Financial support to the institution from the following to conduct clinical trials that I serve as the Principal Investigator for: AstraZeneca, EMD Serono, Galena BioPharma, Genentech. Does not personally receive any funding. C.H. Barrios: Research: Pfizer, Novartis, Amgen, AstraZeneca, Boehringer Ingelheim, Roche, Lilly, Sanofi, GSK, Taiho, Mylan, Merrimack, Merck, Astellas, Bristol-Myers Squibb. Consulting: Boehringer Ingelheim, GSK, Novartis, Pfizer, Roche, Genentech, Eisai, N. Harbeck. My COI is available for ESMO on their internal website. D. Miles: Honoraria for Advisory Boards from Roche-Genentech. S. Saji: Honoraria from AstraZeneca, Chugai Pharmaceutical, Eisai, Novartis Pharma, and research funding from AstraZeneca and Chugai Pharmaceutical. H. Zhang: Consultant for Genentech/Roche from 2015. 2A. Duc: Roche employee and stock. S. Rafii: Employed by Roche. C. Lai: Currently employed by Genentech/Roche and hold company stock. All other authors have declared no conflicts of interest.
also good evidence for the effectiveness of MA as a supportive therapy to ameliorate endocrine therapy-related hot flushes.

**Trial design:** PIONEER is a three-arm, open label, multi-centre randomised phase II pre-surgical window trial evaluating effects of 15 days of preparative therapy with Letrozole (LET) plus MA 40mg, or LET plus MA 160mg in postmenopausal women with newly diagnosed, ER+ HER2- invasive primary breast cancer. Patients are being recruited in Cambridge, with 5-6 other UK sites due to open in q3/4 2017.

### Table: 213TIP 3-arm randomisation

<table>
<thead>
<tr>
<th>Arm</th>
<th>LET 2.5mg daily</th>
<th>LET 2.5mg daily + MA 40mg daily</th>
<th>LET 2.5mg daily + MA 160mg daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm C</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

The primary endpoint is % change in proliferation between baseline and day 15 tumour biopsies, measured by Ki67 immunohistochemical (IHC) assessment. Secondary endpoints include: expression of Aurora Kinase A, Caspase 3 and Androgen receptor/PKR/EMT markers by IHC, and safety endpoints. Exploratory endpoints include: transcription factor mapping (ChIP-seq) on paired fresh frozen tumour samples. Patients are randomised in a 1: 1: 1.5 ratio for arms A, B, C. Based on results from previous clinical trials, a mean 66% reduction in Ki67 is anticipated for LET alone (arm A), and a 77.5% reduction for combination arms B and C, based on preclinical data. A recruitment target of 189 patients is required. Pioneer will help determine if there is value in conducting a follow-on trial designed to investigate the longer term benefit of combining an aromatase inhibitor with MA, and if so, at what dose (40mg vs. 160mg).

**Clinical trial identification:** EudraCT Number: 2016-003752-79 MHEA/REC number: v2.0 5th June 2017

**Legal entity responsible for the study:** Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge

**Funding:** Anticancer Fund

**Disclosure:** All authors have declared no conflicts of interest.

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**213TIP VENTANA (SOLTI-1501): Antiproliferative effect of the addition of oral metronomic vinorelbine to endocrine therapy in luminal/HER2-negative early breast cancer: A window of opportunity trial**

B. Adamo 1, J.A. Perez Fidalgo 2, E. Crueto 1, M. Vidal 1, S. Blanch 2, A. Lopez 1, P. Gomez Parde 2, L. Murillo 1, K. Aramil 1, N. Martinez Jatlev 2, X. Gonzale 1, J. Cans 1, J. Prat 1

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**Background:** The cornerstone of luminal breast tumors treatment both in early and advanced settings is endocrine therapy (ET). Although extended adjuvant ET has demonstrated benefit, a significant percentage of patients relapse. In previous studies, the combination of ET with CDK4/6 inhibitors has shown unprecedented efficacy suggesting that inhibition of the cell cycle in combination with ET is a strategy to keep exploring the efficacy and safety of metronomic VNB has been confirmed in preclinical and clinical studies and it is now considered a multi-mechanisms of action therapy that could offer advantages when combined with other drugs. VENTANA study is a “window of opportunity” trial designed to explore whether, similarly to CDK4/6 inhibitors, this combination could be an alternative to CDK4/6 inhibitors in the treatment of luminal breast cancer patients.

**Trial design:** Pts are randomized (1:1:1) to receive LET 2.5mg daily, oral VNB 50mg 3 days a week, or the combination. After 3 weeks of treatment, pts undergo surgery. Pre-and post-treatment (surgical) samples were analyzed for gene expression. The primary objective is to test if oral metronomic VNB and LET induce a superior antiproliferative effect than either drug alone in pts with early BC defined as Luminal by PAM50. This will be evaluated by the expression of 11 proliferative genes contained in the PAM50 subtype predictor (BIRC5, CCNB1, CDC20, CDC2A1, CEP55, KNTC2, MKI67, PTG1, RRM2, TMY5 and UBE2C) as surrogate signature biomarker of its anticancer activity. In addition, 560 BC-related gene signatures will also be analyzed. Enrollment started in July 2016 in 10 sites across Spain. To date, 47 patients have been included. We expect to report full study results by Spring 2018.

**Clinical trial identification:** NCT02802748

**Legal entity responsible for the study:** SOLTI Breast Cancer Research Funding Group

**Funding:** Pierre Fabre

**Disclosure:** All authors have declared no conflicts of interest.

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**213TIP PALLAS: Palbociclib Colaborative adjuvant study: A randomized phase 3 trial of palbociclib with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy alone for HR+/HER2-negative early breast cancer**

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**Background:** Cell cycle inhibition is a proven target for novel cancer therapeutics. Palbociclib (P) is an orally active inhibitor of CDK4/6, and arrests the cell cycle at the G1-S transition. P in combination with endocrine therapy (ET) has demonstrated efficacy in phase II and III randomized trials for patients with newly diagnosed and recurrent hormone receptor positive HER2 negative (HR+ HER2-) metastatic breast cancer (MBC), and is approved in these settings. Given confirmed benefits of P and ET for MBC, the PALLAS study was designed to determine if the addition of P to adjuvant ET improves outcomes over ET alone in HR+ HER2- early breast cancer.

**Trial design:** PALLAS is an international open-label phase III trial randomizing (1:1) patients (pts) to 2 years of P (125 mg daily, 21 days on 7 days off in a 28-day cycle) combined with at least 5 years of provider choice ET (1L tamoxifen, +/- LHERI agonist), versus ET alone. The primary objective of the study is to compare invasive disease-free survival (iDFS) for the combination of P and ET, versus ET alone. Secondary objectives include comparison of iDFS excluding cancer of non-breast origin, DFS, LRRFS, OS, as well as safety. The principal objective of the translational investigations is to determine the predictive or prognostic utility of defined genomic subgroups with respect to iDFS and OS. Additional objectives include evaluation of JDNA and tissue biomarkers predictive of benefit or resistance, pharmacogenomics, adherence, and patient-reported QOL. Eligible pts are pre- or post-menopausal women or men with stage II-III, HR+, ER+ HER2- breast cancer. Patients may have already initiated ET, but must be randomized within 12 months of diagnosis and 6 months of initiating adjuvant ET. Trial sample size is 4600 pts and stage IIA pts will be capped at a total accrual of 1000 pts. Interim analyses for safety, futility/efficacy and sample size re-estimation are planned. PALLAS opened in 9/2015 and accrual is ongoing. Contact information: emayer@partners.org.

**Clinical trial identification:** US: IND Nr (FDA): 126003 clinicaltrials.gov


**Legal entity responsible for the study:** Alliance Foundation Trials (AFT) LLC for US, ABCSG GmbH for participating countries outside of the US

**Funding:** Pfizer

**Disclosure:** E.L. Mayer, H.J. Burstein, E. Winer: Research funding to the institution from Pfizer. A.M. Demichele: Funding to the institution for clinical trials from Pfizer, Novartis, Genentech and Calithera. Advisory board activities for Pfizer, Novartis and Calithera. M. Koehler, C. Huang Bartlett, X. Huang: Employee and shareholder of Pfizer. M. Grant: Grants and/or personal fees from Sanofi-Aventis, Novartis, Roche, GlaxoSmithKline, AstraZeneca, Nanostring Technologies, Accelers, Pfizer, Smith Medical, outside the submitted work. All other authors have declared no conflicts of interest.
OlympiA: A randomized phase III trial of olaparib as adjuvant therapy in patients with high-risk HER2-negative breast cancer (BC) and a germline BRCA1/2 mutation (gBRCAm)


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Background: In a Phase II study (NCT00494234), treatment with olaparib, a potent, orally-available PARP inhibitor, exerted antitumor activity in patients (pts) with advanced BC harboring a gBRCAm. In a randomized phase III trial, olaparib significantly improved PFS compared to chemotherapy (CT) for patients with HER2-negative gBRCAm advanced BC (OlympiAD, NCT02000622, ASCO 2017). OlympiA (NCT02032823) is a phase III trial of olaparib as adjuvant therapy for pts with high risk gBRCAm HER2-negative BC who have completed local treatment and (neo)-adjuvant CT.

Trial design: OlympiA is a double-blind trial in which high risk HER2-negative pts are randomized (1:1) to receive treatment with olaparib (300 mg tablets bid [2 x 150 mg]) or placebo for 12 months. Eligible pts must have completed local treatment and at least 6 cycles of (neo)-adjuvant containing anthracyclines and/or taxanes. Pts with triple negative BC (TNBC) must have ≥pT2 or ≥pN1 in the adjuvant and non-pCR in the neoadjuvant setting. Pts with hormone receptor (HR) positive BC must have ≥4 positive lymph nodes in the adjuvant and non-pCR and CPS&EG score ≥3 in the neoadjuvant setting. Pts must also harbor a deleterious gBRCAm. Stratification factors include hormone receptor status, prior neoadjuvant versus adjuvant CT, and whether pts have received platinum therapy for current BC. The primary objective is invasive disease-free survival (IDFS). Efficacy assessments will be made by mammograms/breast MRI scans annually for 10 years, beginning 6 months from randomization, and by medical history/physical examination from randomization every 3 months for 2 years, then every 6 months for a further 3 years and annually thereafter. Secondary objectives include overall survival, distant DFS, incidence of new non-BCs, HRQoL, safety and tolerability. The primary IDFS analysis will be performed after 330 IDFS events using a stratified log-rank test. Patient enrolment began in April 2014 and is currently ongoing. The target number for randomization is 1500 patients across ~500 sites and ~25 countries worldwide. Support: U10CA12027,-69651,-37377,-69974,-180868,-180822,-189867; AstraZeneca.

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Legal entity responsible for the study: AstraZeneca

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A gene signature of chemo-immunomutation to predict outcome in patients with triple negative breast cancer treated with anthracycline-based neoadjuvant chemotherapy

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Background: The extent of tumor-infiltrating lymphocytes (TILs) in the residual disease after anthracycline-based neoadjuvant chemotherapy (NACT) is associated with a better prognosis, in patients with triple negative breast cancer (TNBC). We aimed to develop a genomic signature from pre-treatment samples to predict the extent of TILs after NACT, and then to test its prognostic value on survival.

Methods: Using 99 pre-treatment samples (training set), we generated a four-gene signature that predicts post-NACT TIL counts using the LASSO technique. Prognostic value of the signature on survival was first assessed on the training set (n = 99) and then evaluated on an independent validation set including 185 patients with TNBC treated with NACT.

Results: A four-gene signature combining the expression levels of HLF, CXCL13, SULT1E1, and GBP1 predicted the extent of lymphocytic infiltration after NACT. In a multivariate analysis performed on the training set, a one-unit increase in the signature value was associated with distant-relapse free survival (DRFS) (HR = 0.28, 95%CI 0.13, 0.63, p = 0.0018). For the validation dataset, the four-gene signature was significantly associated with DRFS in the entire set (HR = 0.36, 95%CI 0.11, 0.99, p = 0.0256) and in the subset of patients with residual disease (HR = 0.23, 95%CI 0.10–0.55, p = 0.0008).

Conclusions: We developed a four-gene signature of immune-activation, which predicts outcome in patients treated with NACT for TNBC.

Legal entity responsible for the study: Valls et al. Barcelona

Disclosure: All authors have declared no conflicts of interest.

Prognostic estimates of Ki-67 percentage drop after neoadjuvant chemotherapy (NAC) in luminal B (lumB) and triple negative breast cancer (TNBC)

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Background: Pathologic complete response (pCR) and residual cancer burden (RCB) after NAC are validated prognostic markers in BC. We assessed the impact of adding Ki-67% drop (baseline biopsy - surgery) to distant metastasis-relapse free survival (dRFS) models containing CP factors plus post-treatment stage (MDACC CPS score), estrogen receptor status and tumor grade (MDACC CPS + EG score).

Methods: Records from 341 patients (pts) with lumB/HER2 neg (baseline Ki67 > 20%) or TNBC who received NAC from 2008 to 2015 at our hospital were reviewed. Uni- and multivariate Cox models were constructed and concordance-index (c-index) calculated.

Results: Pts median age 47 years (24-83), 60% lumB and 40% TNBC, 62% stage 2, 38% stage 3. pCR: 12% lumB, 32% TNBC (p > 0.01). Median Ki-67% drop: 24% lumB, 5% TNBC (p < 0.01), without differences by NAC regimen. dRFS at 5-year median follow-up was 75% in lumB (CP95% 67-83) vs 62% in TNBC (CP95% 53-74, p = 0.03), 90% in RCB 0/1 (CP95% 91-97) vs 74% in RCB 2/3 (CP95% 65-83, p < 0.01). As compared to pts with RCB 0/1, those with RCB 2/3 plus Ki-67% drop > = 20% (best cut-off in univariate model) had similar dRFS at 5 years (90%, CP95% 81-100, p = 0.48), irrespective of molecular group. Enrichment for Ki-67 > = 20% drop in lumB (60%) vs TNBC (30%, p < 0.01) was observed. Both CPS and CPS + EG scores were validated as independent prognostic factors in univariate dRFS models (c-index of 0.70 and 0.78, respectively). The addition of Ki-67% drop (< = 20% vs > 20%) to CPS and CPS + EG scores in multivariable models significantly improved their performance (c-index of 0.74 and 0.81, respectively). Ki-67 > = 20% drop associates with 70-80% reduction in distant relapse risk (HR 0.27 and 0.16 in CPS and CPS + EG models, respectively, p < 0.05).

Conclusions: Our data support the addition of Ki-67% drop after NAC in lumB and TNBC to existing dRFS online outcome calculators. In the context of RCB 2/3, Ki-67 > = 20% drop is mainly seen in lumB/HER2 neg tumors. Importantly, Ki-67 < 20% drop identifies a high risk population that may be eligible to clinical trials with novel therapeutic interventions in the adjuvant setting.

218P Immune function and response to neoadjuvant chemotherapy in HER2-negative breast cancer

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Background: Gene expression (GE) signatures and Tumor Infiltrating Lymphocyte (TILs) enumeration have shown promise as predictors of response to neoadjuvant chemotherapy in Hormone Receptor negative (HR-) and HER2+, but not in HER2+ HER2- breast cancer (BC). This study aimed to explore their predictive value in HR+/HER2- BC, based on previous work from our group on the association of immune function and chemosensitivity in advanced HR+ BC.

Methods: The PROMIX phase 2 trial enrolled patients with locally advanced HER2- BC to receive six cycles of epirubicin and docetaxel, plus bevacizumab during cycles 3-6. Patients underwent tumor biopsies at baseline and after cycle 2 for GE profiling using DNA microarrays and TIL enumeration according to standard guidelines. Since pathologic complete remission (pCR) is relatively rare in HR+ BC, we also associated an immune gene module score (IMS) and TIL counts with the non-dichotomous variable of decrease in tumor size.

Results: Of the 150 enrolled patients, n = 113 were HR+. For n = 71, both TIL and GE data were available at baseline, while for n = 78 and n = 49 patients longitudinal TIL and GE data at baseline and cycle 2 were available, respectively. At baseline, on both univariate (OR = 2.29, P = 0.037) and multivariate analysis (OR = 2.35, P = 0.044) IMS was associated with pCR, while its association with tumor shrinkage was only apparent on univariate (P = 0.047) and not multivariate analysis (P = 0.061). TIL infiltration >50% (n = 9) was associated with neither pCR (OR = 1.812, P = 0.61) nor tumor shrinkage (P = 0.99). However, decreases in TIL counts in cycle 2 compared with baseline were associated with lesser decreases in tumor size (P = 0.043 for univariate and P = 0.044 for multivariate analysis).

Conclusions: Baseline immune function as assessed by GE analysis, but not TIL enumeration, and a preserved abundance of TILs after chemotherapy were predictive for chemosensitivity at the neoadjuvant setting in patients with HR+, HER2- BC.

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Legal entity responsible for the study: Karolinska University Hospital

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Oncology Department, Bogomolets National Medical University, Kyiv, Ukraine, lower in the control group – 84.7% incidence of distant metastases (diagnosed in 93 (9.34%) cases) was significantly lower than in the main group, and 49.8% in the control group (p < 0.05). Median follow-up was 142 weeks.

**Results:** Achieving negative margins at the area of possible metastasis significantly reduces local recurrence rates, especially in a stage II (5.34%) and III (3.35%) BCP. The incidence of distant metastases (diagnosed in 93 (9.34%) cases) was significantly lower in the main group – 84.7% comparing to the group that had re-resections (4.76%) or the group without microscopic control of margins (8.16%). We tried to understand the causes of local recurrences after BCS, and develop recommendations on achieving safe resection margins.

**Background:** For our first research concerning resection margins in breast-conserving surgery (BCS) for breast cancer patients (BCP) was performed in 2003-2006. In the group of BCP where after positive margins we performed mastectomy (0%), and in the group where the negative margins were achieved immediately (1.27%) the incidence of local recurrences was lower comparing to the group that had re-resections (4.76%) or the group without microscopic control of margins (8.16%).

**Methods:** To clarify the possibility of cancer spreading to the side of regional lymph nodes we were injecting a solution of aqueous methylene in four points around a tumor in 30 minutes before surgery and subsequently we were studying cuts made at the distance up to 5 cm from the tumor margin. In 12% of cases we identified tumor elements in cuts located at a distance of more than 3 cm. In this study we included 996 BCP of I-III stages who had BCS at the National Cancer Institute in 2008-2015. The main group consisted of 379 BCP who had an additional removal of tissues towards the axillary area as a monoblock during the BCS (with additional histological control as mentioned above). 617 in the control BCP in groups of 50.6, 21.1 in the main group, and 49.8, 5.9 in the control group (p > 0.05).

**Conclusions:** BCS with the additional removal of tissues towards the axillary area and lymph nodes dissection as a monoblock is reasonable and significantly reduces local and distant metastases rates. However, more long-term research in this area is urgently needed, especially in terms of benefit in survival.

**Clinical trial identification:** The study is approved by the Commission on issues of ethics of the National Cancer Institute (Protocol No. 7 of 08.04.2010) and the Commission on issues of ethics of the Bogomolets National Medical University (Protocol No. 71 of 10.04.2013).

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**221P A clinically applicable model to predict risk of relapse in patients treated for locally advanced breast cancer: Potential utilization in future clinical trials**

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**Background:** Despite advances in cancer treatment, over 25% of patients (pts) with locally advanced breast cancer (LABC) relapse during first 5 years after treatment. The primary objective was to construct a prediction tool for risk of relapse (RR) in pts with LABC after neoadjuvant therapy (NAT).

**Methods:** This was single center, retrospective study of 546 pts with LABC who received NAT at the Ottawa Hospital Cancer Center between 2005 and 2015. Median follow-up was 49 months. The following data collected: demographics, tumor size, nodal and receptor status, grade, HER-2, stage, treatment and clinical outcomes. Primary endpoints were local and/or distant recurrence rates and time to relapse during the first 5 years. A prediction tool was devised based on the Cox regression model.

**Results:** Over 60 variables were included in primary analysis. Cox regression proportional hazards model analysis resulted in only 5 factors with significant influence on risk of relapse during first 5 years after NAT. Risk factors and their risk prediction value are: 1) residual disease (yes – 4, no – 0), (HR = 4.25, p-value = 0.001), 2) lymph nodes status (positive – 3, negative – 0), (HR = 2.27, p-value = 0.006), 3) Inflammatory histology (yes – 2, no – 0), (HR = 1.90, p-value = 0.003), 4) estrogen receptors status (positive – 2, negative – 0), (HR = 2.07, p-value = 0.001), 5) Adjuvant chemotherapy (yes – 6, no – 1), (HR = 1.76, p-value = 0.036). When these factors are combined the following Relapse Prediction (RP) Score can be constructed. According to this simple RP score, patients can be classified into three groups (RP score – 0, 0.5 – 6, 6 – 12). RR was 7 times higher in patients with RP Score 8-12 vs patients with score 0-0.5 (p-value = 0.001).

**Conclusions:** Patients with LABC represent a heterogeneous group with diverse risk of disease recurrence that can be predicted. Patients with high risk may require additional treatment and/or more active follow-up strategies and this simple model may be used to design unique studies in LABC based on RP score.

**Disclosure:** All authors have declared no conflicts of interest.

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**222P Role of radiotherapy and its impact on survival of male breast cancer: Experience from a tertiary cancer center**

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**Background:** Male breast Cancer (MBC) is a rare disease accounting for about 1% of all malignancies in men and 1% of all breast cancers. These patients(pts) are managed like female breast cancers. There is limited literature available defining the role of radiotherapy (RT) in management of MBC. We conducted a retrospective analysis to study the impact of adjuvant RT on outcome of MBC pts treated at our centre.

**Methods:** Review of MBC pts presenting to our centre from 2005 to 2015 was done. All underwent pre-treatment evaluation in a combined tumor clinic comprising radiation, surgical and medical oncologist. Most pts were treated with surgery followed by adjuvant chemotherapy and kept on regular follow up. Overall survival (OS) was defined as time from pathologic diagnosis to last follow up or death. Disease free survival (DFS) was defined as time from diagnosis to first relapse.

**Results:** 96 pts of MBC were identified. Median age was 58 years (range 28-83). Clinical stage I, II, III and IV were 8, 27, 39 and 22 respectively. 60% of pts with known receptor status, 83% were ER positive, 82% PR positive, 20% Her-2/neu positive and 7.5% triple negative. 69 pts underwent modified radical mastectomy or wide local excision. 54% were pathologically node positive. Adjuvant RT was delivered to 34% pts at 1.82 Gy fraction to a median dose of 50 Gy (range 45-60 Gy). Radiation field comprised of chest wall (5%) + regional nodes (25%). Median follow-up was up to 24 months (range 9-132). 16 pts had relapse out of which 4 had local and 13 had distant (most common site bone) metastases after a median duration of 19 months. 2 yr estimated DFS for the entire cohort was 79.2% and 2 yr OS was 85.7%. The 2 yr DFS in pts undergoing surgery was 86.4% vs 29.2% in those who did not (p = 0.001). Pts who received adjuvant RT had better 2 yr DFS (92.4% vs 52.9%, p = 0.002). Adjuvant chemotherapy did not significantly affect the 2 yr DFS (93.1% vs 73%, p = 0.125). Conclusions: MBC mostly present in advance stages at our centre and harbor HR positive disease with low HER-2 overexpression. Adjuvant RT provided a statistically significant improvement in outcome. Longer follow up of these cohort of pts is required for accurate evaluation of role of RT in MBC.

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The association between HR+ status (single versus double HR+ ) and pCR rates compared to HR negative patients remained the same in subgroup analyses of HER2+ and HER2 negative patients separately. No difference in DFS was seen between the 3 subgroups of patients: HR negative, single and double HR+ patients.

Conclusions: BC patients with single HR+ disease behave differently than double HR+ patients in terms of likelihood of achieving pCR after neoadjuvant chemotherapy and do not differ from HR negative patients. This difference does not translate into a difference in DFS. Prospective studies are needed to validate these findings before considering different treatment strategies for these 2 subgroups of HR+ BC patients.

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**Legal entity responsible for the study:** The Department of Breast Tumours at the National Cancer Institute

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**Background:** This study aims to evaluate the current state of multiple primary malignant neoplasms (MPMN) in Ukraine and develop decision criteria for type of surgical treatment for these patients.

**Methods:** The study included 2,032 patients who received special treatment at the Department of Breast Tumours at the National Cancer Institute in 2008-2015. Among them there were 195 MPMN patients where 107 (54.9%) presented synchronous cancer (SC) and 88 (45.1%) presented metachronous cancer (MC). The average age of patients was 46.6 years, and the number of postmenopausal women was 63.1%. Among SC patients there were 68 (36.1%) with only breast localizations and 47 (43.9%) with combination of breast and other localizations (gynaecological etc.). In MC there were 46.6% with only breast localizations and 47 (53.4%) with combination of breast and other localizations. All the patients were evaluated in terms of aggressiveness of the disease, survival rates, as well as risk factors and treatment options.

**Results:** The clinical course of the disease (CCD) in MPMN patients was worse in SC patients compared to MC patients (p = 0.00026). A more aggressive CCD was observed in patients exposed to radiation from the Chernobyl accident (p = 0.000798). There was no influence on CCD of such factors as primary localization, type of surgical treatment and age of patient. However, the impact of type of surgery was statistically proven, i.e. CCD in patients who underwent mastectomy was worse comparing to patients who underwent breast-conserving surgery (p = 0.00048). Plastic and reconstructive surgery in SC patients was statistically proven as reasonable increasing overall survival by 29% (p = 0.015). There was an influence of local recurrences on the overall survival in SC patients reducing it by 71% (p = 0.033), however, there was no influence in MC cases.

**Conclusions:** The MPMN patients have got an improved attentive management and treatment. Medical and surgical oncologists should concern all the risk factors that have influence on CCD in these patients and provide the best option of management. The research in this area of oncology is open and this is crucial to continue researches for better outcome of these patients.

**Clinical trial identification:** The study is approved by the Commission on issues of ethics of the National Cancer Institute (Protocol No. 7 of 08.04.2010) and the Commission on issues of ethics of the Bogomolets National Medical University (Protocol No. 71 of 10.04.2013).

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A decade of HER2-targeted therapy in older patients with invasive breast cancer at Institut Curie

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Background: Around 40% and 20% of breast cancers (BC) occur in women aged ≥65 and ≥75 years respectively. Although HER2-targeted therapy has profoundly improved the management of HER2+ BC, literature is short of data for frail and elderly patients reflecting the poor representation of older patients in registration trials.

Methods: We conducted a retrospective analysis of any stage HER2+ BC patients aged ≥65 years treated with a HER2-targeted therapy at Institut Curie between 2000 and 2012 to assess treatment feasibility. Baseline data were extracted from the institution database and patients’ files were reviewed for treatment compliance and safety profile.

Results: From 2000 to 2012, 261 and 76 patients received anti-HER2 treatment in adjuvant and metastatic setting respectively. In adjuvant setting (age distribution 65-69/70-74/75+ years: 109/90/67, median follow-up 65 months), the median duration of trastuzumab treatment was 12 months with an 80% completion rate (defined as ≥9 months of treatment) decreasing significantly ≥75 years (70%). Grade ≥3 cardiac toxicity occurred in 9/6% of patients, was reversible in 72% of cases, and multivariate analysis identified the following risk factors for cardiac events: history of thrombembolic disease, valvulopathy and performance status (PS) ≥2 [OR 6.3 (95% CI: 1.4-27.7), 25.6 (4-162.8) and 18.2 (1-304.3) respectively], but not age. In metastatic setting (age distribution 65-74/75+ years: 41/35, median follow-up 27 months), median duration of HER2-targeted therapy was 22.8 months (0-109.2), with no impact of age. Trastuzumab and lapatinib (alone or in combination) were mostly prescribed, pertuzumab and T-DM1 representing <15% of cases depending on treatment line. Multivariate analysis identified the following factors for mortality: PS ≥2, history of thrombembolic disease [OR 3 (95% CI: 1.1-8.1) and 3 (1.7-16.3) respectively], but not age.

Conclusions: HER2-targeted therapy seems feasible ≥65 yrs patients in both adjuvant and metastatic setting. Cardiac toxicity occurs in 10-15% but is reversible in most cases. Chronological age does not seem to affect duration of anti-HER2 treatment nor cardiac toxicity.

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Dedicated breast PET to predict pathological complete response after neoadjuvant chemotherapy for breast cancer

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Background: Reports indicate that whole-body (WB) 18F-fluorodeoxyglucose (FDG) PET can predict a pathological complete response (pCR) after neoadjuvant chemotherapy (NAC). New dedicated breast PET (DBPET) can generate high-resolution images and thus might be able to predict pCR after NAC. The present study aimed to determine whether or not DBPET can predict the effects of NAC for breast cancer more effectively than WBPET.

Methods: The clinical responses of 35 consecutive patients with breast cancer (T1-4, N0-1, M0) who underwent NAC between January 2016 and January 2017 were assessed using WBPET and DBPET. We assessed maximum standardized uptake value (SUV(max), before (pre-SUV(max)) and after (post-SUV(max)) NAC and rates of change in SUV(max) before and after NAC. Relationships between these parameters and pathological responses (pCR) were assessed using each modality. We created receiver operating characteristics curves (ROC), calculated areas under them (AUC) for both WBPET and DBPET images and predicted pCR.

Results: Twelve of 35 patients achieved pCR. The median pre-SUV(max), post-SUV(max) and ASUv(max) among the 35 patients determined using WBPET and DBPET were 6.8 and 18.0, 1.7 and 3.1, and 78.2 and 77.6, respectively. The uptake ratio of 18F-FDG was indistinguishable from background in WBPET, but confirmed in DBPET after NAC in three of 23 patients with non-pCR disease. The median pre-SUV(max) of WBPET and DBPET in the pCR group was higher than non-pCR group (7.88 and 21.73 vs 6.22 and 16.28, p = 0.30 and p = 0.15 respectively). In contrast, post-SUV(max) of the pCR group was lower than non-pCR group (0.97 and 2.86 vs 1.54 and 8.46, p = 0.062 and p = 0.032 respectively). ASUv(max) of pCR group was higher than non-pCR group (82.35 and 88.56 vs 76.34 and 72.55, p = 0.27 and p = 0.04, respectively). Additionally, the AUC of DBPET (pre-SUV(max): 0.543, post-SUV(max): 0.725, ASUv(max): 0.752) was higher than WB PET (pre-SUV(max): 0.477, post-SUV(max): 0.694, ASUv(max): 0.534) in either time points.

Conclusions: The diagnostic accuracy of DBPET was equal to, or better than those of WB PET. DBPET might serve as a new diagnostic modality for breast cancer. All planning therapeutic strategies for patients with breast cancer after neoadjuvant chemotherapy.

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Pregnancy associated breast cancer spotlights

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Background: Pregnancy associated breast cancer (PABC) is a rare entity of breast cancer. It is defined as breast cancer occurring during pregnancy or within 12 months from end of pregnancy. Though rare, it represents a very challenging situation to both the physician and patient. This retrospective study is an attempt to focus on PABC cases presenting at our institute regarding their personal, disease characteristics and type of treatment received.

Methods: This is a retrospective study conducted at Kafr-Al-Ainy oncology center “NEMROCK”. The files of female patients diagnosed with breast cancer under the age of 40 in the period from January 2005 to December 2014 were retrospectively reviewed. A comparison was conducted and extracted between PABC cases and non-pregnant cases concerning personal and disease characteristics, modality of treatment and outcomes.
Results: This study included a total of 175 patients 40 years old or younger, among them 40 were PABC cases. Twenty-five percent of PABC patients presented with distinct metastasis at first presentation while only 11.6% of the non-pregnant patients presented with metastasis (p < 0.0001). Time from onset of symptoms till breast cancer diagnosis was more than 6 months in 55.6% of PABC cases in comparison to 36.3% in non-pregnant cases (p-value 0.043). Concerning treatment; 32.4% of PABC cases received neoadjuvant chemotherapy while 20.7% of non-pregnant patients received it (p-value 0.027). There was no statistical difference in personal and disease characteristics between pregnant and non-pregnant patients including family history, pathological subtypes, stage, grade and biological subtypes. There was no statistically significant difference in disease free survival between PABC cases and non-pregnant ones (p-value 0.497).

Conclusions: PABC is associated with a late diagnosis. Although PABC patients present at later stages than non-pregnant ones and the use of neoadjuvant treatment is higher in pregnant cases, the outcome of patients with PABC is comparable to that of non-PABC of matched age.

Legal entity responsible for the study: Karal deainty department of oncology
Funding: None
Disclosure: All authors have declared no conflicts of interest.

Clinical trial identification: EUDRACT number: 2016-001432-35 ClinicalTrials.gov, NCT02819518

Legal entity responsible for the study: Merck & Co., Inc., Kenilworth, NJ, USA
Funding: Merck & Co., Inc., Kenilworth, NJ, USA

Background: The insulin-like growth factor (IGF) and the cyclin D1-cyclin-dependent kinase (CDK) 4/6-retinoblastoma pathways have been implicated in the pathogenesis and resistance mechanisms of a variety of cancers, including HR+/HER2- BC and NSCLC. IGF-ligand dependent signalling via the IGF receptor results in upregulation of cyclin D1, and thus, progression through the cell cycle, providing rationale for the simultaneous inhibition of IGF and CDK4/6. This trial assesses the maximum-tolerated dose (MTD), safety and preliminary efficacy of the IGF-ligand-neutralising antibody, xentuzumab, in combination with abemaciclib, a selective inhibitor of both CDK4 and 6, +/- hormone therapy, in pts with solid tumours.

Trial design: Study BI 1280.18 (NCT03099174) is a Phase Ib multicentre, non-randomised, open-label, dose escalation trial with four dose-finding cohorts (Cohorts A–D) followed by two expansion cohorts (Cohorts E, F). Eligible pts include adults ≥ 18 yrs (≥ 20 yrs for Japan), with measurable or evaluable disease, adequate organ function and an ECOG performance status of 0 to 1. Other inclusion criteria include prior (≤ 2) chemotherapeutic regimens for metastatic disease and disease progression on prior anti-hormonal therapies. The primary endpoint of the study is the recommended phase II dose (RPSD) of XEN and abemaciclib.

Clinical trial identification: NCT03099174

Legal entity responsible for the study: Merck & Co., Inc., Kenilworth, NJ, USA
Funding: Merck & Co., Inc., Kenilworth, NJ, USA
function, ECOG PS ≤ 1, and unresectable advanced or metastatic solid tumours after failure on standard therapy (Cohort A), postmenopausal locally advanced or metastatic HR+, HER2- BC (Cohorts B–D, F), or stage IV NSCLC after 1–2 lines of therapy and failure after platinum-based chemotherapy (Cohort E); CDK4/6 inhibitor-naïve pts (Cohorts A–D) and pts who have received prior CDK4/6 inhibitors (palbociclib or ribociclib) plus aromatase inhibitors (Cohort F) are included. Pts will receive either xentuzumab plus abemaciclib alone (Cohorts A, E) or in combination (at MTD defined for the doublet therapy) with letrozole (Cohort B), anastrozole (Cohort C), or fulvestrant (Cohorts D, F). Primary endpoints are the MTD and/or recommended phase-2-dose (RP2D; Cohorts A–D), and objective response (Cohorts E, F). Further endpoints include antitumour activity (Cohorts E, F), and pharmacokinetic outcomes (all Cohorts). This study will be conducted in the US, Europe and Japan. Pt screening is planned to start May 17; target enrolment: N=88.

Clinical trial identification: NCT03099174; 1280.18

Legal entity responsible for the study: Boehringer Ingelheim

Funding: Boehringer Ingelheim

A phase II trial of pan-HER inhibitor Pocitotinib, in patients with HER2-positive metastatic breast cancer who have received at least two prior HER2-directed regimens: The results of NOV120101-203 trial


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Background: Although the introduction of HER2 directed therapy including trastuzumab, pertuzumab, lapatinib, and TDM-1 in the treatment of HER2-positive metastatic breast cancer (MBC) patients favorably changed the natural history of this disease, HER2-positive MBC will eventually progress in most patients. Pocitotinib is a novel, oral pan-HER kinase inhibitor which showed potent anti-tumor activities through irreversible inhibition of HER family tyrosine kinases.

Methods: This open-label, multicenter phase 2 study was designed to evaluate the efficacy and safety of pocitotinib monotherapy in patients with HER2-positive MBC who have progressed from more than 2 HER2-directed therapies. Patients received pocitotinib 12 mg once daily on a 14-day on/7-day off schedule. Dose escalation up to 16 mg was allowed at appropriate time point and dose reduction to 8–10 mg were performed according to toxicities. Progression-free survival (PFS) as the primary endpoint and objective response rate (ORR), overall survival (OS), and safety were evaluated.

Results: From Apr 2015 to Feb 2016, 106 patients were enrolled in the trial from 7 institutes in Korea. The patients were median age of 50 (range: 30–76) who had received median 4 prior anti-cancer therapies including median 2 HER2-directed therapies in the advanced or metastatic setting. Median follow up duration was 12 months. The median PFS was 4.04 months (95% CI, 2.94–4.40 months), and median overall survival has not been reached. The disease control rate was 75.49% (77/102) including 20 patients with confirmed partial response. The most common treatment-related AEs were (total/grade ≥3) diarrhea (96.23%/14.15%), stomatitis (92.45%/12.26%), and rash (63.21%/3.77%).

Conclusions: Pocitotinib showed meaningful clinical activity in heavily-treated HER2-positive MBCs. Diarrhea and stomatitis were the major toxicities leading to dose modification. Biomarker study being analyzed from pre- and on-treatment biopsies is warranted to support further on the meaningful clinical outcomes of pocitotinib in HER2-positive MBC.

Clinical trial identification: NCT02418689

Legal entity responsible for the study: National OncoVenture & Hanmi Pharmaceutical Co., Ltd.

Funding: Hanmi Pharmaceutical Co., Ltd.

Disclosure: All authors have declared no conflicts of interest.
Methods: Between 4 Apr 2014 and 22 Jan 2016, 707 pts with HER2+ MBC were randomized to 1:1 to PF-0528014 or trastuzumab-EU, both given with paclitaxel (starting dose 80 mg/m², days 1, 8, 15 of each 28-day cycle). Trastuzumab was administered weekly until at least Week 35 (first dose 4 mg/kg, subsequent doses 2 mg/kg), with treatment continuing until progression. The primary endpoint was objective response rate (ORR; complete or partial response according to RECIST 1.1) by Week 25 and confirmed by Week 35, based on blinded central radiology review. Secondary endpoints included safety, measures of tumor control, immunogenicity, and PK.

Results: The risk ratio for ORR was 0.910 for PF-0528014 over trastuzumab-EU, with a 0.842–1.049 confidence interval, which was within the pre-specified equivalence margin of 0.8–1.25. 1-yr progression-free survival (56% for PF-0528014 vs 52% for trastuzumab-EU) and 1-yr survival (88.84% vs 87.96%) were similar between groups. The safety profile, including incidence of serious adverse events, was similar in both arms, and no new safety signals were identified. After study drug initiation, all pts received negative for antitumor antibodies, except 1 pt receiving trastuzumab-EU. Up to cycle 5 day 8, mean trough and peak serum concentrations were similar for both agents. At the cutoff for this primary analysis (24 Aug 2016), 558 pts remained ongoing in the study.

Conclusions: In pts receiving first-line treatment for HER2+ MBC, PF-0528014 was similar to trastuzumab-EU in terms of efficacy, safety, immunogenicity, and PK.

Clinical trial identification: NCT01989676, EudraCT number: 2013-001532-34

Legal entity responsible for the study: Pfizer Inc

Funding: This study was sponsored by Pfizer Inc.

Disclosure: M. Pegram: Consulting: Pfizer Inc; A. Ocana Fernandez1, M. Ruiz Borrego2, M. Gil Martin3, S. Antolin4, M. Atienza2, N. Ribelles5, A. Guerrero6, M. Muiñiz, J. Fernández-Pérez, E. Carrasco, F. Rozo, A. Pandelita, Vana, F. Hilton, C. Zacharchuk, R. Ewuesudo: Employee of and holds stock or stock options in Pfizer Inc. All other authors have declared no conflicts of interest.

239PD A phase II trial of dasatinib (D) in combination with trastuzumab (T) and paclitaxel (P) in the first line treatment of HER2 positive metastatic breast cancer (MBC) patients (pts): GEICAM/2010-04

A. Ocana Fernández1, M. Ruiz Borrego2, M. Gil Martin3, S. Antolin4, M. Atienza2, N. Ribelles5, A. Guerrero6, M. Muñiz, J. Fernández-Pérez, E. Carrasco, F. Rozo, A. Pandelita, Vana, F. Hilton, C. Zacharchuk, R. Ewuesudo: Employee of and holds stock or stock options in Pfizer Inc. All other authors have declared no conflicts of interest.

Background: In HER2 overexpressing MBC around 40% of pts treated with T-based regimens do not respond and half of them progress within a year. The combination of the SRC inhibitor D and T is synergistic in preclinical models. We conducted a phase II trial combining D with a standard first line treatment with T/P.

Methods: Pts with HER2+ MBC (by central laboratory) were included. First line treatment consisted of 28-day cycles of T 2mg/kg weekly, P 80mg/m2 (3 weeks on 1 week off) and D 100mg once daily administered in first line until radiologic or symptomatic progression (PD) or unacceptable toxicity. Primary objective was objective response rate (ORR); secondary objectives were safety, other efficacy variables (Clinical Benefit Rate, CBR), Time to Progression (TTP), Progression Free Survival (PFS) and pharmacodynamic biomarkers (Phosphorylated (p)-AKT, and p-SRC) in peripheral mononuclear cells (PBMCs).

Results: Twenty-nine pts were included; median age was 49 years (31-81), 12 pts (41%) were premenopausal, 22 (76%) had hormone-receptor positive tumors and 23 (79%) had visceral disease. The median number of cycles was 12 (1-35), 9 pts discontinued treatment due to PD, 6 for adverse events, 6 due to investigator/holder criteria and 8 due to other reason. The ORR was 79.3% (95% CI 60.3-92.2) and the CBR was 82.8% (95% CI 64.3-94.2). Median TTP was 23.9 months (95% CI 14.8-Not reached (NR)) and median PFS was 23.9 months (95% CI 10.3-NR). The mean relative dose intensity was seen in 10.3% (n = 5) and 24.1% (n = 7) of pts. No G3 toxicity was seen. G3 toxicities were limited to fatigue, hypertension, neutropenia and thrombocytopenia (6.9% [n = 2] each). Phosphorylated SRC and AKT were reduced in PBMCs after 8h (4.4 and 1.9 folds, respectively) of D administration in cycle 1 day 1 in 16 assessed pts.

Conclusions: D can be safely combined with T and P and the combination is effective with a ORR that reached almost 80% of patients. We observed decreased levels of p-SRC and p-AKT in PBMCs in patients treated with D, as previously described in preclinical models.

Clinical trial identification: NCT01306942

Legal entity responsible for the study: GEICAM Spanish Breast Cancer Group

Funding: Bristol-Myers Squibb (BMS)

Disclosure: All authors have declared no conflicts of interest.

240PD Comprehensive genomic profiling of primary and metastatic CDH1 mutated classic and pleomorphic invasive lobular breast carcinomas reveals markers of hormonal therapy resistance and opportunities for targeted therapies

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Background: Although invasive lobular breast cancer (ILC) is typically combined with the far more frequent ductal disease for clinical trials and research studies. We queried whether classic (CILC) and its uncommon pleomorphic variant (PILC) featured unique genomic alterations (GA) which could influence therapy for patients with relapsed and refractory disease.

Methods: From a series of 10,784 invasive breast carcinomas DNA was extracted from 40 µm of FFPE sections of 434 (4%) CDH1 mutated ILC including 428 classic (CILC) (94%) and 26 pleomorphic (PILC) (6%) subtypes. CGP was performed on hybridization-captured, adaptor ligation-based libraries (mean coverage depth >60X) for up to 315 cancer-related genes. Total mutational burden (TMB) was determined on 1.2 Mbp of sequenced genome.

Results: Median age at 63 years was similar for both CILC and PILC (see Table). Clinical ER+ status (p) was higher in CILC and HER2+ status was higher in PILC (P = 0.0001). ESRI substitution GA were significantly higher in CILC and the frequency of ESRI GA was significantly higher in CILC exposed to hormonal therapy (me-tastasis biopsies) than in pre-treatment primary tumors (P < 0.0001). ERBB2 GA (amp + non-amp) detected by CGP were higher in PILC than CILC in both pre-and post-treatment samples (P < 0.001 for both). ERBB2 GA nearly doubled after hormonal treatment in both CILC and PILC. PIK3CA GA were similarly the most frequent GA in both CILC and PILC, but TP53 GA were significantly more frequent in PILC than CILC. Median TMB was higher in PILC than CILC and TMB ≥ 15 mut/Mb was more than twice as frequent in PILC than CILC (P = 0.0146). Patients with post primary ther-apy associated ESRI and ERBB2 GA responding to precision therapies will be presented.

Table 2:40PD CILC (428) PILC (26)

| Median Age | 63 | 63 |
| ESR1 GA Primary Pre-Rx | 6% | 0% |
| ERBB2 GA Post-Metastatic Post-Rx | 10% | 0% |
| PIK3CA (53), CCND1 (21), TP5 (17), ARID1A, AKT3, MDMM, PTEN (all 11%) | 7% | 18% |
| PTEN (all 11%) | 34% |
| TMB median (mut/Mb) | 2.7 | 3.6 |
| TMB ≥ 15% | 8% | 19% |

*when clinical status available.

Conclusions: Both CILC and PILC show differences in GA in pre-treatment primary vs metastatic lesions in important genes such as ERBB2 and ERBB2 likely reflecting the impact of primary therapies. Relapsed CILC is more often driven by ESRI GA and PILC by ERBB2 GA. Both the CILC and PILC groups have subsets with high TMB, more frequent in PILC, indicating potential for immunotherapies for these patients.

Legal entity responsible for the study: Jeffrey S Ross

Funding: None
Initial results of a phase 1 dose expansion cohort of M6620 (formerly VX-970), an ATR inhibitor, in combination with cisplatin in patients with advanced triple-negative breast cancer NCT02157792

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Background: ATR is a regulator of the cellular response to replication stress and signals DNA damage repair through homologous recombination. Many cancers depend on ATR to survive DNA damage. VX-970 is a potent, selective inhibitor of ATR with pre-clinical anticancer activity in combination with DNA-damaging chemotherapy in TNBC models. Given the prevalence of DNA damage repair defects in TNBC, this study evaluated the safety and efficacy of VX-970 in combination with Cis in an expansion cohort of pts with BRCA1/2 wild-type mTNBC.

Methods: Eligible pts had advanced ER- PR- and HER2- BC with 0-2 prior non-platinum-based therapies. First line pts were eligible if relapse occurred ≥ 3 months after prior (neo)adjuvant chemotherapy. Measurable disease per RECIST 1.1 was required. OVAR 16 pts planned for enrollment ≥ 30 were required to be BRCA1/2 germline wild-type and to have basaloid molecular subtype tumors on central testing. Pts received intravenous Cis 75 mg/m² on day 1 with VX-970 140 mg/m² on days 2 and 9 of each 21-day cycle. In pts intolerant to Cis or at investigator discretion, treatment could be switched to carboplatin AUC 5 with VX-970 90 mg/m².

Results: At the time of this analysis, 35 female pts with mTNBC who received ≥ 3 cycles of study drug were included in the safety set (median age, 48 y [range 35-74 y]). Grade ≥ 3 adverse events included diarrhea (24% vs 2%), hyperglycaemia (13% vs 0%) and neutropenia (11% vs 9%). Discontinuation rates due to adverse events were 15% on AZD and 7% on placebo. Conclusions: Adding AZD to weekly paclitaxel did not prolong PFS in the overall population or PIK3CA subgroup of ER+/HER2- advanced or metastatic breast cancer.

Clinical trial identification: ClinicalTrials.gov NCT01625286 Other Study ID Numbers: D3610C00002; 2011-006312-31 (EudraCT Number).

Legal entity responsible for the study: AstaZeneca

Funding: Vertox Pharmaceuticals Incorporated

Disclosure: M.L. Telli: Advisory role for AstraZeneca, PharmaMar, Tesaro, and Vertex, and contracted research with Calithera, Genentech, Medivation, Oncosec, Pfizer, Pharmamar, Tesaro, and Vertex. E. Dean: Employee of AstraZeneca. Research funding from Vertox. S.M. Tolany: Research funding from Genentech, Merck, Pfizer, Novartis, Lilly, Exelixis, Nekter, and AstraZeneca. R. Tang, M.S. Penney, G. Conboy, S.Z. Fields: Employee of Vertoxt Pharmaceuticals Incorporated and may own stock or stock options in that company. J. Pollard: Employee of Vertoxt Pharmaceuticals Limited and may own stock or stock options in that company. G. Shapiro: Research funding from Vertex and Pfizer. Advisory role for Vertex, G. Therapeutics, Lilly, Millennium, Takeda, Tesaro, Chugai, and EMD Serono. All other authors have declared no conflicts of interest.
**Legal entity responsible for the study: AstraZeneca**

**Funding:** AstraZeneca

**Disclosure:** S. Delaloge: Honoraria, research funding, consulting, and travel, expenses and accommodation from Novartis, Roche, AstraZeneca, Pfizer, Genentech, and Lilly.

**Olaparib monotherapy in OlympiAD led to a doubling of ORR vs TPC**

**Results:** 302 patients were randomized to olaparib (n = 201) or single-agent TPC (capecitabine, eribulin or vinorelbine). Patients had 2 or more lines in the metastatic setting. Patients were randomized 2:1 to olaparib and standard single-agent chemotherapy of the physician’s choice.

**Methods:** OlympiAD was a randomized, open-label, Phase III study of olaparib monotherapy in HER2-negative metastatic breast cancer (mBC) and a germline BRCA mutation receiving olaparib monotherapy over chemotherapy treatment of physician’s choice (TPC). Hazard ratio (HR) was 0.58 (95% CI 0.46, 0.81) P < 0.001; 7.0 vs 4.2 months for olaparib vs TPC, respectively.

**Background:** The Phase III OlympiAD study (NCT02000662) in patients with metastatic breast cancer (mBC) and a germline BRCA mutation receiving olaparib monotherapy vs standard single-agent chemotherapy treatment of physician’s choice

**Table 243PD Subgroup analyses for PFS by baseline tumour burden and location are shown in the Table.**

<table>
<thead>
<tr>
<th>Tumour burden</th>
<th>Olaparib 300 mg bid</th>
<th>Chemotherapy</th>
<th>TPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 metastatic site, n</td>
<td>46</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>8.4</td>
<td>4.2</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.62 (0.35, 1.13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2 metastatic sites, n</td>
<td>159</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>6.5</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.59 (0.43, 0.82)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Tumour location**

| Bone-only metastases, n | 16 | 6 |
| Median PFS, months | 11.2 | – |
| HR (95% CI) | Not calculated |
| Other metastatic sites, n | 189 | 91 |
| Median PFS, months | 6.6 | 3.9 |
| HR (95% CI) | 0.60 (0.46, 0.81) |

*Includes both bone and other tumour locations*

**Conclusions:** Olaparib monotherapy in OlympiAD led to a doubling of ORR vs TPC and a larger reduction in target lesion size, indicating a more pronounced depth of response in HER2-negative BRCA-mutation positive patients with measurable disease, objective response rate (ORR) was 59.9% for olaparib monotherapy vs 30.3% for TPC, respectively. We report further efficacy outcomes for objective response, target lesion shrinkage and tumour burden.

**Table 243PD Subgroup analyses for PFS by baseline tumour burden and location are shown in the Table.**

**Conclusions:** Eligible patients (pts) were randomized to olaparib (300 mg bid) or placebo (PLB) with cabazitaxel (50 mg/m² q3w). All pts had 1L mCRPC with increasing PSA level, MDSD ≤ 1 month and ≥ 2 measurable lesions. The primary endpoint was PFS, assessed locally. In addition, a symptomatic skeletal event (SSE) and OS were assessed.

**Methods:** There were 2 randomization stages: stage 1 (150 patients) to confirm the equivalence between olaparib and PLB and (243 patients) thereafter, 2:1 randomization to olaparib or placebo.

**Background:** The BOLERO-4 study demonstrated clinical benefit and an acceptable safety profile with first-line (1L) EVE + LET in postmenopausal pts with ER+/HER2– advanced breast cancer (ABC). Progression-free survival (PFS) subgroup analyses in BOLERO-4

**Table 244PD**

**Results:** At the data cut-off (Dec 17, 2016), 202 pts with ABC were enrolled for 1L treatment with EVE + LET. Median PFS and 18- and 24-month Kaplan–Meier estimated PFS rates were similar to the FAS (irrespective of pt age, presence/absence of visceral metastases, or presence/absence of bone-only lesions at baseline). The distribution and frequency of all-grade adverse events (irrespective of causality) among pts aged <65 years and ≥65 years was comparable with the overall population.

**Conclusions:** Treatment benefit with EVE + LET in the 1L setting was maintained across pt subgroups and was consistent with that observed in the FAS of the BOLERO-4 study. EVE + LET, therefore, is an effective 1L treatment for ER+, HER2– ABC, irrespective of pt age, visceral metastases, or bone-only lesions. These data support the potentially important role of EVE in the ABC treatment landscape.

**Clinical trial identification:** Protocol version 04

**Legal entity responsible for the study:** Novartis Pharmaceuticals Corporation

**Funding:** Novartis Pharmaceuticals Corporation

**Disclosure:** T. Bachot: Research funding from Roche, Novartis. Consultant for and travel expenses from AstraZeneca, Roche, Novartis, Pfizer. M. Royce: Research funding and honoraria from Novartis. C. Villanueva: Advisory board member for Novartis Pharmaceuticals Corporation. F. Melo Cruz: Research funding from Novartis, Janssen, Roche, Celgene. Travel, accommodation, expenses from Janssen. C. Falkson: Research funding from Novartis, Oncotherapy, Genentech, EMD Serono. Consultant for and honoraria from Biotheranostics. J. Jeong: Research funding from Dting-A, Boehringer-Ingelheim.
Postmenopausal women (N = 501) with measurable disease, 135 (53%) vs 91 (37%) pts had a com-
ponent of patients with HER2-negative, incurable, metastatic or unresectable locally
advanced breast cancer (ABC). RIB prolonged PFS and was associated with a greater degree of tumor shrinkage vs
LET.

Clinical trial identification: NCT01958021

Legal entity responsible for the study: Novartis Pharmaceuticals Corporation

Funding: Novartis Pharmaceuticals Corporation

Disclosure: W. Janni: Research grants and/or honoraria from Sanofi-Aventis, Novartis, Roche, Pfizer, AstraZeneca, Chugai, GSK, Eisai, Cellgene, Johnson & Johnson. T. Bachelor: Research funding from Roche and Novartis; Consultant for AstraZeneca, Roche, Novartis, and Pfizer; travel from AstraZeneca, Roche, Novartis, Pfizer. F.J. Esteve: Research funds and consultancy/honoraria from Novartis. T.I. Pluard: Advisor for Novartis. S. Sutradhar: Novartis employee and Novartis shares. M. Miller: Novartis employee and Novartis stocks/shares. M. Campone: Consultant/advisory role for Novartis, Pfizer, AstraZeneca, Roche, and Lilly. All other authors have declared no conflicts of interest.

Conclusions: In postmenopausal women with HR+, HER2- ABC, first-line RIB + LET prolonged PFS and was associated with a greater degree of tumor shrinkage vs PRO + LET.

Table: 245PD

<table>
<thead>
<tr>
<th>Q</th>
<th>Cut-off</th>
<th>Corresponding best % change in tumor size</th>
<th>N=231</th>
<th>n=212</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤Q1</td>
<td>≤25%</td>
<td>At least –53%</td>
<td>73 (32%)</td>
<td>38 (18%)</td>
</tr>
<tr>
<td>Q1–Q2</td>
<td>&gt;25% to ≤50%</td>
<td>Between –53% and –33%</td>
<td>64 (28%)</td>
<td>52 (25%)</td>
</tr>
<tr>
<td>Q2–Q3</td>
<td>&gt;50% to ≤75%</td>
<td>Between –33% and –12%</td>
<td>52 (23%)</td>
<td>54 (25%)</td>
</tr>
<tr>
<td>&gt;Q3</td>
<td>&gt;75%</td>
<td>Less than –12%</td>
<td>42 (18%)</td>
<td>68 (32%)</td>
</tr>
</tbody>
</table>

Efficacy of two times versus continuous eight cycles of paclitaxel/bevacizumab as first-line chemotherapy in metastatic breast cancer: The Stop&Go study of the Dutch Breast Cancer Research Group (BOOG)

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Background: The primary goal of this non-inferiority trial was to determine if an inter-
mittent treatment regimen was not inferior to a continuous regimen, in first-line treat-
ment of patients with HER2-negative, incurable, metastatic or unresectable locally
advanced breast cancer.

Methods: Patients were randomised to receive 8 cycles or 2x4 cycles of paclitaxel/beva-
cizumab on days 1, 8 and 15 every 4 weeks, both with continuation of bevacizumab

Clinical trial identification: NCT02145758

Legal entity responsible for the study: Sanofi

Funding: Sanofi

Disclosure: A. Claassen: Research grants and/or honoraria from Chugai, Roche, Novartis, Pfizer, AstraZeneca, Chugai, GSK, Eisai, Cellgene, Johnson & Johnson, Pfizer. M. Lopez-Yurdak: Research grants and/or honoraria from AstraZeneca, Chugai, Pfizer.

Conclusions: In patients with HER2-negative, incurable, metastatic or unresectable locally
advanced breast cancer, the intermittent treatment regimen was not inferior to the con-
tinuous arm, according to the primary endpoint of TTF-I.

Table: 245PD

<table>
<thead>
<tr>
<th>FAS</th>
<th>Age</th>
<th>Visceral metastases</th>
<th>Bone-only lesions at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of PFS events, n (%)</td>
<td>Median PFS (95% CI), months</td>
<td>Kaplan-Meier-estimated PFS rate, % (95% CI) 18-month</td>
<td>Kaplan-Meier-estimated PFS rate, % (95% CI) 24-month</td>
</tr>
<tr>
<td>No. (n=202)</td>
<td>N=108</td>
<td>N=94</td>
<td>n=123</td>
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<tr>
<td>No. of PFS events, n (%)</td>
<td>108 (53.5)</td>
<td>68 (63.0)</td>
<td>40 (42.6)</td>
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<tr>
<td>Median PFS (95% CI), months</td>
<td>22.0 (18.1–25.1)</td>
<td>20.3 (16.5–23.9)</td>
<td>24.0 (18.4–29.7)</td>
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<tr>
<td>Kaplan-Meier-estimated PFS rate, % (95% CI) 18-month</td>
<td>58.8 (50.9–65.8)</td>
<td>54.6 (44.2–63.8)</td>
<td>64.6 (52.1–74.6)</td>
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<tr>
<td>Kaplan-Meier-estimated PFS rate, % (95% CI) 24-month</td>
<td>42.9 (35.0–50.5)</td>
<td>40.0 (30.0–49.7)</td>
<td>46.7 (33.8–58.6)</td>
</tr>
</tbody>
</table>

No. of PFS events, n (%) 108 (53.5) 68 (63.0) 40 (42.6) 65 (52.8) 43 (54.4) 12 (42.9) 96 (55.2) 108 (53.5) (35.0–50.5) (33.8–58.6) 65 (52.8) (33.5–53.5) 43 (54.4) (29.5–53.6) 12 (42.9) (25.7–67.7) (33.9–50.4)

CI, confidence interval; NE, not estimable.
once every 21 days until disease progression or unacceptable toxicity. If progressive disease occurred ≥ 3 months after the initial 4 cycles with paclitaxel/bevacizumab in the intermitent arm, another 4 cycles were given. If progressive disease occurred in the continuous arm or < 3 months after the initial 4 cycles in the intermittent arm, second-line treatment was started. The primary endpoint was progression-free survival (PFS), secondary endpoints included overall survival (OS). Intention-to-treat and per-protocol analyses were performed using a proportional hazards regression model. The two-sided 95% confidence interval (CI) for the hazard ratio (HR) was calculated and the upper limit was compared with the non-inferiority margin of 1.34.

Results: The intention-to-treat population comprised of 420 patients. The total median PFS in first-line treatment was 10.7 months (95% CI 9.7 - 12.6) for the intermittent regimen and 9.7 months (95% CI 8.4 - 10.2) for the continuous regimen (HR for disease progression or death [intermittent vs. continuous], 1.086; 95% CI 0.743 - 1.631). Results on OS were similar with a HR of 1.312 (95% CI 0.959 - 1.794). The per-protocol analysis showed comparable results. Safety results and actually delivered treatments did not reveal unexpected findings and will be presented at the meeting.

Conclusions: Intermittent first-line treatment with paclitaxel/bevacizumab is not non-inferior to continuous scheduling regarding PFS in patients with HER2-negative incurable locally advanced or metastatic breast cancer. Analysis of the secondary endpoint OS supported this conclusion. Therefore, intermittent first-line treatment cannot be recommended over continuous scheduling.

Clinical trial identification: EuroCT 2010-01519-18, BOOG 2010-02

Legal entity responsible for the study: Dutch Breast Cancer Research Group (BOOG)

Funding: F. Hoffmann-La Roche Ltd, The Netherlands, TEVA Nederland B.V.

Disclosure: V. Tran-Heijen: Financial support from the Dutch Breast Cancer Research Group during the conduct of the study; Grants and non-financial support from Roche/Pfizer/ Novartis/AstraZeneca, grants from Esaï, outside the submitted work. F. Erdkamp: Advisory board Roche. All other authors have declared no conflicts of interest.

A single-arm, phase ii study assessing the efficacy of pembrolizumab (pembo) plus radiotherapy (RT) in metastatic triple negative breast cancer (mTNBC)


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Background: Overall response rates of 13-19% have been reported with checkpoint inhibitor monotherapy in chemotherapy-resistant, PD-L1-positive mTNBC. RT is frequently used to enhance local control in mTNBC and has been reported to induce distant (abscopal) tumor responses when combined with immunotherapy. In this study we evaluate the safety and efficacy of RT combined with the anti-PD-1 inhibitor, pembo, in a single-arm, two-stage, phase II study in mTNBC.

Methods: Eligible women had biopsy-proven mTNBC, EOCOG performance status 0-2, and ≥2 measurable sites of metastatic disease with at least 1 site requiring RT. A total RT dose of 5000 Gy was delivered in 5 daily fractions. IV pembo was given at 20mg/kg on days 1, 8, and 15 of RT. RT was given every 3 weeks until disease progression. The primary endpoint was overall response rate at week 13 in the non-irradiated lesions by RECIST v1.1. Secondary endpoints included safety and overall survival. Tumor biopsies were obtained at baseline and at week 7. PD-L1 expression was not required for study entry.

Results: As of May 1, 2017, the study has completed enrollment (N = 17) with 4 women on treatment pending 13-week evaluation. Median age was 52y (range 37-73y). Median number of prior therapies received for metastatic disease was 3 (range 0 to 8). Of the 7 women not evaluable at 13 weeks: 5 died secondary to disease-related complications (at weeks 3, 6, 7, A, and 9) and 2 came off study due to disease progression prior to week 13. Of the 6 women evaluable at week 13, 2 (33%) had a partial response (PR), 1 (17%) had stable disease (SD) and 3 (50%) had disease progression. The 2 PRs represented 76% and 79% decreases in tumor burden by RECIST 1.1 durable for 21 and 31 weeks, respectively. SD response was durable for 30 weeks. Common toxicities were mild and included fatigue, myalgia and nausea.

Conclusions: The combination of pembo and RT was well-tolerated. This is a poor prognosis population with ≤3 (38%) evaluable patients dying within 12 weeks of study entry. However, durable responses were observed outside of the RT field in 2/6 (33%) patients who were unselected for PD-L1 expression and evaluable at 13 weeks. Safety and toxicity data for all study patients will be presented.

Clinical trial identification: NCT02730130

Legal entity responsible for the study: Memorial Sloan Kettering Cancer Center Funding: Merck

Disclosure: H.L. McArthur: Advisory boards for Celgene, Merck, OBI Pharma, Spectrum, Syndax, Roche, Peregrine, Calithera, Eli Lilly and TapImmune. Research supported by Bristol Myers Squibb; Eli Lilly; MedImmune; LLC/AstraZeneca; and Merck. C.A. Barker: In the past year has received research funding from Elekta, Merck, and AmaGen; honoraria from Driver Group, a biotechnology company; and served as a Pfizer advisory board consultant. A. Gucalp: Research funding from Pfizer and Innocrin related to other work in triple negative breast cancer. A. Ho: Research funding by Merck. All other authors have declared no conflicts of interest.

Table: 248P

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<th>Pt characteristics</th>
<th>Prior ET n = 249</th>
<th>No Prior ET n = 195</th>
<th>Prior CT n = 213</th>
<th>No Prior CT n = 231</th>
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<tr>
<td>Median age, y</td>
<td>60</td>
<td>64</td>
<td>58</td>
<td>65</td>
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<tr>
<td>White/Asian race, %</td>
<td>75/17</td>
<td>81/11</td>
<td>77/16</td>
<td>78/14</td>
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<tr>
<td>Non-Hispanic or Latino, %</td>
<td>87</td>
<td>87</td>
<td>86</td>
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<tr>
<td>Median duration since diagnosis, y</td>
<td>8.8</td>
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<td>8.8</td>
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<td>Exposure to P</td>
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<td>Median number of cycles (range)</td>
<td>18 (1-37)</td>
<td>21 (1-37)</td>
<td>19 (1-37)</td>
<td>21 (1-37)</td>
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<tr>
<td>Median treatment duration, m (range)</td>
<td>16.66 (0.03-33.84)</td>
<td>20.76 (0.07-34.07)</td>
<td>18.89 (0.03-34.07)</td>
<td>20.37 (0.07-33.18)</td>
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<td>Median average daily P dose, m (range)</td>
<td>125 (77-125)</td>
<td>125 (78-125)</td>
<td>125 (77-125)</td>
<td>125 (78-125)</td>
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<tr>
<td>EF’c asymmetric endpoints for P + vs PBO +L</td>
<td></td>
<td></td>
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<tr>
<td>Median PFS, mo Hazard ratio (95% CI)</td>
<td>22.2 vs 11.3 0.53 (0.40-0.70)</td>
<td>25.7 vs 19.6 0.63 (0.44-0.90)</td>
<td>22.4 vs 13.7 0.53 (0.40-0.72)</td>
<td>25.7 vs 17.0 0.61 (0.44-0.84)</td>
</tr>
<tr>
<td>Objective response rate, % Odds ratio (95% CI)</td>
<td>31.7 vs 27.0 1.38 (0.84-2.29)</td>
<td>52.8 vs 44.8 1.38 (0.82-2.33)</td>
<td>36.2 vs 30.3 1.30 (0.78-2.22)</td>
<td>47.6 vs 38.9 1.34 (0.88-2.32)</td>
</tr>
<tr>
<td>Rate of clinical benefit, % Odds ratio (95% CI)</td>
<td>81.5 vs 66.2 2.31 (1.31-3.70)</td>
<td>89.2 vs 75.0 2.76 (1.37-5.56)</td>
<td>81.7 vs 70.6 1.85 (1.04-3.29)</td>
<td>87.9 vs 69.9 1.32 (1.71-5.17)</td>
</tr>
</tbody>
</table>

NF=not estimable.
Conclusions: An association between ORR and OS was observed. Responders have a better OS compared to nonresponders.

Clinical trial identification: NCT02102490

Legal entity responsible for the study: Eli Lilly and Company

Funding: Eli Lilly and Company


240P

A global phase III clinical study comparing NK105 and paclitaxel in metastatic or recurrent breast cancer patients


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Background: Paclitaxel (PTX) is a standard chemotherapy drug for metastatic or recurrent breast cancer (mR/C). However, it presents problems such as hypersensitivity and peripheral sensory neuropathy (PSN). NK105 is a novel nanoparticle drug delivery formulation that encapsulates PTX in polymeric micelles. In a murine model, passive targeting was shown and NK105 accumulated in tumors. We expected NK105 to have similar efficacy and a better safety profile, regardless of hypersensitivity and PSN, compared with PTX, considering a previous phase II study in gastric cancer patients (pts). This study aimed to verify the non-inferiority of NK105 to PTX in terms of progression-free survival (PFS) in mR/C pts.

Methods: Eligible pts were randomly assigned at a 1:1 ratio to either the NK105 (N) or PTX (P) arm. NK105 (65 mg/m²) and PTX (80 mg/m²) were administered via intravenous infusion weekly for 3 weeks followed by a 1-week rest period until disease progression. Tumor responses were assessed every 6 weeks by RECIST Ver. 1.1. The primary endpoint was PFS, while the secondary endpoints were overall response rate (ORR), overall survival (OS), and safety. PSN was evaluated by CTCAE Ver. 4.03 and FACT/GOG-NTX Ver. 4 (FACT).

Results: From September 2012 to July 2014, 436 pts were randomized and 422 pts were included in the efficacy analysis. The median PFS (95% CI) for the N and P arms was 256 (212–302) and 260 days (211–350), respectively. The adjusted hazard ratio (95% CI) was 1.255 (0.989–1.592), exceeding the set non-inferiority margin. The ORR was 10% in the N arm and 10.1% in the P arm. PSN incidences in the N and P arms were 52.8% and 70.6%, respectively and incidence of Grade 3 or more was lower in the N arm than in the P arm pts. Cumulative PSN incidences between the N and P arms were significantly different (P = 0.01) and were favored in the N arm.

Conclusions: The efficacy of 65 mg/m² of NK105 could not be verified in terms of non-inferiority of PFS relative to PTX in this study. NK105 safety profile was generally similar to that of PTX, but the NK105-PSN profile was better than that of PTX. NK105 efficacy should be re-evaluated in future studies.

Legal entity responsible for the study: Nippon Kayaku Co., Ltd.

Funding: Nippon Kayaku Co., Ltd.
Efficacy and safety of olaparib combined with eribulin in patients with advanced or metastatic triple negative breast cancer (TNBC) previously treated with anthracyclines and taxanes: The final analysis of a Japanese phase I/II trial


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Background: Prognosis of metastatic TNBC is poorer compared with those of other subtypes because of the lack of effective treatment target. TNBC contains molecularly heterogeneous phenotypes, some of which are influenced by germline (g) BRCA1/2 mutation. Eribulin is one of standard treatments for metastatic TNBC and olaparib (Lynparza®; Avel parole®) with PARP (poly ADP ribose polymerase) inhibitor, has shown remarkable efficacy in BRCA mutated breast cancer. Therefore, we evaluated the efficacy and safety of the combination of these drugs in a phase I/II trial (UMIN00009498) with an expectation of synergistic effect.

Methods: In phase I, we have determined the recommended dose as 300mg bid of olaparib twice daily and 1.4mg/m² of eribulin intravenously on day 1 and 8 in 21-day cycle. The primary efficacy endpoint in phase II was tumor response rate (RR) in the central review. The planned size was 24, with one-sided alpha of 0.1; power of 0.8, expected RR of 0.3 and threshold of 0.1.

Results: Twenty-four patients were enrolled from June 2014 to December 2014 in phase II. The median age was 46 years old (range: 27 to 73). The median number of prior chemotherapy regimens was 3 (range: 2 to 6). Sixteen patients (66.7%) had visceral metastasis and 8 had non visceral metastasis. Dose intensity of eribulin was 0.69 (mg/m²/week) and that of olaparib was 208.6 (mg/week). RR in central review was 29.2% (90%CI: 17.0-44.2), including 7 with PR, 7 with SD, 7 with PD and 3 with NE; thus, the null hypothesis was rejected. In institutional decision, RR was 37.5% (95%CI: 6.4, 19.5), including 1 patient with CR. Median progression-free survival was 4.2 months (95%CI: 3.0 to 7.4). Median overall survival was 14.5 months (95%CI: 4.8 to 22.0). Safety was analyzed separately for phase I and II. Significantly severe adverse events (≥ grade 3) were leukopenia (87.5%, 83%), neutropenia (87.5%, 83.3%), febrile neutropenia (20.8%, 33.3%), anemia (16.7%, 41.7%) and thrombosis (0%, 8.3%), respectively.

Conclusions: The combination of olaparib and eribulin was well tolerated and showed a promising efficacy and safety for metastatic TNBC.

Clinical trial identification: release date: 31/03/2017 (In Japanese)

Legal entity responsible for the study: National Cancer Center Hospital (National Cancer Center Hospital Arnau Vilanova, Valencia, Spain, 12Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA. 13Eli Lilly and Company, Madrid, Spain, 14Oncology Clinical Development, Eli Lilly and Company, Paris, France, 15Medical Oncology Service, Partners Healthcare, Boston, MA, USA.


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Disclosure: All authors have declared no conflicts of interest.

Abemaciclib plus fulvestrant in patients (pts) with HR+/HER2- endocrine therapy naïve (EN) advanced breast cancer - an exploratory analysis of MONARCH 2


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Background: MONARCH 2 demonstrated that the addition of abemaciclib, dosed on a continuous schedule at 150 mg twice daily, to fulvestrant (F) significantly improved progression-free survival (PFS) and objective response rate (ORR) compared to placebo (P) plus F (PFS hazard ratio (HR), 0.553; P<0.00001; ORR in measurable disease 48% vs 21.3%; P<0.001) in women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC) who had progressed on endocrine therapy (ET). Here we present efficacy and safety findings from an exploratory cohort of EN pts from MONARCH 2 not included in the initial analysis. EN pts from MONARCH 2 were randomized 2:1 to receive abemaciclib+ F (500 mg, per label) or F alone.

Methods: EN pts were randomized 2:1 to receive abemaciclib+ P (F) or P alone. Pts were eligible if at least 27/45 (60%) patients are progression free at 3 months.

Results: As of 27 April 2017, 45 of 45 pts are enrolled; 39 are evaluable at 3 months and 6 have not had 3-month evaluation. At 3 months, 30/39 (77%) are progression free (1 CR, 8 PR, 21 SD); 9 pts progressed. There are no cardiac or febrile neutropenic events detected (3 grade 3 neutropenia and 1 grade 4 vomiting) and the study was amended to lower initial G dose to 1000 mg/24h. The preliminary 3 month-PFS is 77% in evaluable pts (95% CI 62% to 87%). The updated 3 month-PFS results will be presented. Combination of P beyond progression is associated with apparent clinical benefit. A randomized trial is justified to confirm this clinically important observation.

Clinical trial identification: NCT02252887

Legal entity responsible for the study: Memorial Sloan Kettering Cancer Center Funding: Genentech/Roche

Disclosure: All authors have declared no conflicts of interest.
and neutropenia. Diarrhea generally occurred in the early cycles and was managed with dose adjustment and conventional anti-diarrheal medication.

Conclusions: In this exploratory cohort of EN pts, the addition of abemaciclib to fulvestrant demonstrated a comparable increase in PFS and consistent safety results to those observed in the ITT population in MONARCH 2.

Clinical trial identification: NCT02107703

Legal entity responsible for the study: Eli Lilly and Company

Funding: Eli Lilly and Company


Matching-adjusted indirect treatment comparison of ribociclib and palbociclib as first-line treatments for HR+, HER2- ABC

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Background: Ribociclib (RIB) and palbociclib (PAL) combinations with letrozole (LET) vs LET alone have been evaluated in separate Phase 3 randomized controlled trials in patients with hormone receptor-positive (HR+) breast cancer (ABC); however, no head-to-head comparative studies have been conducted. Classic indirect treatment comparison (ITC) can lead to biased results due to differences in patient populations and trial designs. These differences can be corrected by using the matching-adjusted indirect comparisons (MAIC) technique. Here, we compare RIB and PAL in patients with HR+, HER2- ABC using MAIC.

Methods: Individual patient data were available for the RIB trial (MONALEESA-2). As only published summary data were available for the PAL trial (PALOMA-2), RIB data were adjusted to closely match the PAL data. Data for RIB-treated patients were assigned weights so that weighted mean baseline characteristics matched those reported for PAL. Overall survival data have not been reported for PALOMA-2, thus only progression-free survival (PFS) data were compared. Adjusted hazard ratios (HRs) for PFS were calculated using weighted Cox regression models and used to calculate indirect HRs with 95% confidence intervals (CIs). Classic frequentist ITC was performed before and after adjustment. ITC of Grade 3/4 adverse events (AEs) was also performed.

Results: The unadjusted PFS HR (95% CI) for RIB vs LET was 0.556 (0.429; 0.721) and for PAL-LET vs LET was 0.580 (0.460; 0.720). MAIC adjustment for age, race, region, Eastern Cooperative Oncology Group status, disease stage at diagnosis, sites of metastasis and chemotherapy setting at baseline provided a RIB vs LET HR estimate of 0.501 (0.365; 0.688). The HR for unadjusted ITC of RIB vs PAL was 0.959 (0.681; 1.350) and by MAIC was 0.864 (0.586; 1.274). ITC of Grade 3/4 AEs yielded a risk ratio (RR) of 0.81 (0.61; 1.08) for RIB vs PAL.

Conclusions: Using MAIC methodology due to a lack of head-to-head trials, the resulting HRs for PFS were comparable. Similarly, using ITC, AE profiles were also comparable although the RR for AEs slightly favored RIB.

Legal entity responsible for the study: Novartis Pharmaceuticals Corporation

Funding: Novartis Pharmaceuticals Corporation

Disclosure: A. Foryszyte: Consultant for Novartis. D. Chandwana, M. Monaco: Novartis employee and stock/share. All other authors have declared no conflicts of interest.

Efficacy of palbociclib plus fulvestrant in advanced Hormone Receptor-positive (HR+) metastatic breast cancer (MBC) pretreated with everolimus: Real-life data from the French temporary authorization for use (TAU) at the Institut de Cancérologie de l’Ouest

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Background: The CDK4-6 inhibitor palbociclib, combined with hormonal therapy is a new standard of treatment for HR+ Metastatic Breast Cancer. Before the European Medicines Agency approval, a Temporary Authorization for Use (TAU) has been set up in France restricted to patients pretreated with everolimus. We present the efficacy data of this combination in this population.

Methods: Between November 2015 and November 2016, all the patients treated with palbociclib + fulvestrant according to the TAU in our institution were prospectively included. Data from their medical records and adverse events (AE) were collected.

Results: 60 patients received at least one dose of palbociclib in combination with fulvestrant with a median age of 61 years. 50 patients (83.3%) had visceral metastasis and 10 (16.7%) had bone only disease. Patients had an average of 5.3 lines of treatment before palbociclib initiation, including hormonal therapy (mean = 3.0) and chemotherapy (mean = 2.3). Of note, 28 patients (46.7%) had received fulvestrant previously and all had been pretreated with everolimus. With a median follow-up of 8.1 months, median progression free survival (PFS) was 6.1 months (95% CI, 4.2 to 7.4) and median overall survival was not reached. PFS was the same according to the presence of visceral metastasis or not (HR 1.46 (95% CI, 0.57 to 3.74), p = 0.42).

Interestingly, patients treated previously with fulvestrant and subsequently re-challenged with fulvestrant had a PFS of 6.4 months, which was similar to patients who didn’t receive fulvestrant previously (HR = 1.00 (95% CI 0.55 to 1.83), p = 1.00). The most common AE were neutropenia (n = 53), thrombocytopenia (n = 25) and anemia (n = 20). At the time of this analysis (April 2017), 36 patients received a further line of treatment after progression.

Conclusions: In this heavily pretreated population, the association of fulvestrant plus palbociclib provides an interesting median PFS of 6.1 months. Patients previously treated with fulvestrant seem to derive the same magnitude of benefit compared to fulvestrant naive patients.

Legal entity responsible for the study: Institut de Cancérologie de l’Ouest

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Phases of BYL719 therapy and its effects on patient outcomes.

BYL719 is an oral inhibitor that selectively targets the 

PI3K in Japanese patients with advanced solid malignancies


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Background: BYL719 is an oral inhibitor that selectively targets the PI3K in Japanese patients with advanced solid malignancies.

A phase 1 study of BYL719, an isoretinoin selective PI3K inhibitor, in Japanese patients with advanced solid malignancies


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Background: BYL719 is an oral inhibitor that selectively targets the PI3K in Japanese patients with advanced solid malignancies.

Annals of Oncology

257P Phase 1 study of RX-5902, a novel orally bioavailable inhibitor of phosphorylated P68, which prevents β-catatin translocation in advanced solid tumors

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Clinical trial identification: NCT01387323

Legal entity responsible for the study: Novartis Pharmaceuticals KK, Tokyo, Japan

Disclosure: H. Saka: Grants from Novartis, KH, Daitchu Sanyo, Merck, Eisai, Bristol-Myers Squibb, Taiho, Ono, Chugai, Eli Lilly, Bayer, MSD, Quintiles, West JCOG.

Personal fees: Chugai, Kyorin, NU, BI, Eli Lilly, Astellas, NoPharma, IRE, Ono, Chunchi Shimbun, Taiho. S. Takahashi: Grants from Novartis, during the conduct of the study; grants from Chugai, grants from Astrazeneca, grants from Daiichisankyo, grants from Bayer, grants from Parexel, outside the submitted work. K. Nakano, T. Kakuizumi: Personal fees from Novartis Pharmaceuticals KK, during the conduct of the study. Y. Ando: Grants and personal fees: Chugai, Takeda, KHK, Eisai, Taiho, Nippon, YakultHonzyo, Mochida, Merck, Ono, Eli Lilly, Novartis, Janssen, Hisamitsu, GSK, Terumo, Bayo, Meiji, RSC, Boehringer Ingelheim, Bristol-Myers Squibb, Sasa, Otsuka, Shinogi, outside the submitted work. All other authors have declared no conflicts of interest.

Annals of Oncology

258P Adherence to International ESO-ESMO (ABC) guide-lines in HER2-ve metastatic breast cancer (MBC) patients (pts): Preliminary results of the Glim 13 - AMBRA Study


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Background: ESO/ESMO develops consensus guidelines for MBC treatment every 2 years, potentially applicable worldwide. Aim of the present analysis is to verify the adherence to ABC recommendations for HER2-ve MBC in the context of the AMBRA study.

Methods: AMBRA is a longitudinal cohort study, aiming to describe the choice of first-line therapy in all evaluable cases. We selected 4 statements from the ABC1 & ABC2 Conferences, comparing them with the clinical choices of 1st-line therapy in all evaluable cases.

We selected 4 statements from the ABC1 & ABC2 Conferences, comparing them with the clinical choices of 1st-line therapy in all evaluable cases.
Background: Two prognostic models “bioscore” and “Neo-bioscore” were recently published and validated to help predict the outcomes of patients with non-metastatic breast cancer treated with either upfront surgery or upfront neoadjuvant chemotherapy. A comparable model for metastatic disease is yet to be developed. The current study thus sought to propose and validate a third model “M-bioscore” to help predict the outcomes of treatment-naive patients with metastatic breast cancer.

Methods: Through SEER*Stat program, surveillance, epidemiology and end results (SEER) database (2010-2013) was accessed. The resulting cohort was equally split into two halves: training set (to guide model development) and validation set (to test the model prediction). Multivariate analysis for the candidate prognostic factors (extent of metastases, estrogen receptor (ER), progesterone receptor (PR), HER2 neu and nuclear grade) was conducted through a Cox proportional model. M-bioscore was then calculated for each patient. Cancer-specific survival analyses according to M-bioscore were conducted through Kaplan-Meier analysis/log-rank testing.

Results: A total of 6655 patients with previously untreated metastatic breast cancer and complete data were identified in the period from 2010-2013. The following factors were associated with better cancer-specific survival in multivariate analysis in the training set (isolated distant nodal metastases, ER positivity, PR positivity, HER2 neu positivity and lower nuclear grade) (P < 0.01). This has been shown for both training and validation sets. Accordingly, the M-bioscore model has been proposed as follows: an M-bioscore score of 7 corresponds to metastases in bone, 6 to liver and lung, 5 to bone and liver, 4 to bone and lung, 3 to liver and lung, 2 for liver, lung and lymph nodes, 1 for lymph nodes. A total M-bioscore was then calculated for each patient. Cancer-specific survival was compared according to the score. Log rank testing with pair wise comparisons between all different scores was conducted. For cancer-specific survival assessment according to the M-bioscore, Pvalues for pair wise comparisons among different score points were significant (P < 0.05) except for the comparison between score 0 and score 1. Score of 2-4 was compared in the training cohort. These findings have been confirmed in the validation and overall cohorts. Table shows the three year cancer-specific survival (CSS) rates for patients in the overall cohort according to M-bioscore.

Conclusions: M-bioscore is a novel, easy and reliable tool for predicting the outcomes of patients with previously untreated metastatic breast cancer. Further external validation within the context of other population-based cohorts is recommended.

Legal entity responsible for the study: Omar Abdel-Rahman

Legal entity responsible for the study: Marina E. Cazzaniga

Funding: Celgene Ltd.

Disclosure: All authors have declared no conflicts of interest.

260P Three-year cancer-specific survival according to M-bioscore

<table>
<thead>
<tr>
<th>M-bioscore</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>CSS rate</td>
</tr>
<tr>
<td>0-2</td>
<td>22 (3.3%)</td>
</tr>
<tr>
<td>3-4</td>
<td>273 (4.1%)</td>
</tr>
<tr>
<td>5-6</td>
<td>1567 (23.5%)</td>
</tr>
<tr>
<td>7-8</td>
<td>1202 (18.1%)</td>
</tr>
<tr>
<td>9-10</td>
<td>1680 (25.2%)</td>
</tr>
<tr>
<td>11-12</td>
<td>1038 (15.6%)</td>
</tr>
<tr>
<td>13-14</td>
<td>590 (8.9%)</td>
</tr>
<tr>
<td>15-16</td>
<td>283 (4.3%)</td>
</tr>
</tbody>
</table>

Funding: None

Disclosure: All authors have declared no conflicts of interest.

261P Is PFS a more relevant endpoint than OS in 1L HR+, HER2- MBC? A systematic literature review

A. Forsythe1, D. Chandiwana2, J. Barth3, M. Thabane4, J. Baek5, A. Shor6, G. Tremblay1

1Purple Squirrel Economics, New York, NY, USA, 2Oncology, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA, 3Oncology, Novartis Pharma GmbH, Nuremberg, Germany, 4Oncology, Novartis Pharmaceuticals Canada Inc., Danval, QC, Canada

Background: Hormone receptor-positive (HR +), human epidermal growth factor receptor-negative (HER2-) metastatic breast cancer (MBC) accounts for 73% of all MBC. Endocrine therapy (ET) is the basis of first-line (1L) therapy for patients (pts) with HR +, HER2- MBC; however, efficacy is limited by ET resistance. Novel therapies have demonstrated improvements in progression-free survival (PFS) vs standard ET. The clinical relevance of PFS is debated due to a lack of direct correlation with overall survival (OS) benefit, and cases of asymptomatic progression. We review studies of HR +, HER2- MBC to assess factors that influence OS and treatment response, and changes in health-related quality of life (HRQoL).

Methods: The Embase®, MEDLINE®, and Cochrane databases were systematically searched to identify studies in adult women with HR +, HER2- MBC, published 2006-January 2017, and written in English. Phase (Ph) 2 and 3 randomized controlled-trials (RCTs), observational, and retrospective studies were considered and HRQoL and real-world evidence reviewed.

Results: 79 RCTs were identified: 58 (73%) in the 1L setting and 21 (27%) in the ≥2-line setting. PFS data were reported in 61 (77%) studies; 31 (51%) reported significant PFS improvement. OS was reported in 44 (56%) of studies; only 11 (14%) reported a significant OS improvement. Significant improvements in both PFS and OS were reported in only 6 (8%) studies (1 Ph 2; 5 Ph ≥3). Pts with HER2– MBC received on average ≥5 lines of therapy, with no defined treatment pathway. Baseline characteristics, prior therapies, and the type and number of post-progression therapies significantly impacted OS. PFS, response rates, and HRQoL decreased with each line of therapy (EQ-SD: 0.78 1L vs 0.70 post-progression).

Conclusions: Multiple HR +, HER2- MBC therapies have been investigated yet few CTS have achieved a significant improvement in OS. Multiple factors besides the choice of 1L therapy impact OS, such as post-progression therapies, which cannot be controlled in RCTs. This study emphasizes the importance of PFS improvement coupled with HRQoL maintenance in 1L treatment of HR+, HER2- MBC. 1. Howlader N et al. J Natl Cancer Inst 2014;106:404-55.

Legal entity responsible for the study: Novartis Pharmaceuticals Corporation

Funding: Novartis Pharmaceuticals Corporation

Disclosure: A. Forsythe: Consultant for Novartis. D. Chandiwana, M. Thabane, J. Baek: Novartis employee and Novartis stocks/shares. J. Barth: Novartis employee. All other authors have declared no conflicts of interest.

PFS/TPP as a potential surrogate for OS in HR+, HER2- MBC

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Background: Several, recent randomized controlled trials (RCTs) in hormone receptor-positive (HR +), human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer (MBC) have demonstrated a significant improvement in

Table: 259P Adherence to ABC recommendations for HER2-ve pts

<table>
<thead>
<tr>
<th>M-bioscore</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/% (adherence)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>160/270 (59.2%)</td>
</tr>
<tr>
<td>1</td>
<td>270/21.8%</td>
</tr>
<tr>
<td>2</td>
<td>431/20.6%</td>
</tr>
<tr>
<td>3</td>
<td>431/27.6%</td>
</tr>
</tbody>
</table>

Table: 260P Three-year cancer-specific survival according to M-bioscore

<table>
<thead>
<tr>
<th>M-bioscore</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
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<td>590 (8.9%)</td>
</tr>
<tr>
<td>15-16</td>
<td>283 (4.3%)</td>
</tr>
</tbody>
</table>
progression-free survival (PFS); however, few have reported an improvement in overall survival (OS). OS may be an imperfect endpoint due to the impact of factors such as baseline characteristics and subsequent therapies. Investigation of the use of PFS or time to progression (TTP) as a surrogate for OS in HR+ or HER2- MBC has been limited. This study assesses the correlation of PFS/TTP and OS in HR+ or HER2- MBC across all lines of therapy.

**Methods:** A systematic literature review of RCTs in HR+, HER2- MBC was conducted to identify studies that reported both median PFS/TTP and OS. The correlation between PFS/TTP and OS was evaluated using Pearson’s product-moment correlation and Spearman’s rank correlation. Subgroup analyses were performed to explore possible reasons for heterogeneity. Errors-in-variables weighted least squares regression (ELSR) was used to model incremental OS months as a function of incremental PFS/TTP months. An exploratory analysis investigated the impact of 3 covariates (chemotherapy vs other, PFS vs TTP, and IL vs > IL) on the use of PFS/TTP in OS prediction. The lower 95% prediction band was used to determine the minimum incremental PFS/TTP months below which there would be no predicted OS benefit (the surrogate threshold effect [STE]).

**Results:** A total of 39 studies were identified. There was a statistically significant correlation between median PFS/TTP and OS (Pearson = 0.741, p < 0.000; Spearman = 0.650, p < 0.000). Results were unchanged for chemotherapeutic and hormonal or targeted therapy, and for line of therapy. Initial LSR analysis yielded an R² of 0.354; 1 PFS/TTP month corresponded to 1.13 OS months. The addition of 3 covariates improved R² to 0.560; 1 PFS/TTP month corresponded to 0.78 OS months. The STE for OS benefit was 5.6–6 months of incremental PFS/TTP.

**Conclusions:** The results of this study indicate a significant association between PFS/TTP and OS, which may justify the use of PFS/TTP as a surrogate for OS benefit during regulatory approval and subsequent reimbursement of new therapies in HR+ or HER2- MBC.

**Legal entity responsible for the study:** Novartis Pharmaceuticals Corporation

**Funding:** Novartis Pharmaceuticals Corporation

**Disclosure:** A. Forsythe: Consultant for Novartis. D. Chandiwana, M. Thabane, I. Baeck: Novartis employee and Novartis stock/share. I. Barth: Novartis employee. All other authors have declared no conflicts of interest.

### Table: 263P

<table>
<thead>
<tr>
<th>5-Year OS (%)</th>
<th>Mean Per-Patient OS (Months)</th>
<th>Population Life Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>38.8</td>
<td>55.3</td>
</tr>
<tr>
<td>1995</td>
<td>9.9</td>
<td>27.2</td>
</tr>
<tr>
<td>Difference</td>
<td>-28.9</td>
<td>+28.1</td>
</tr>
</tbody>
</table>

**Legal entity responsible for the study:** Genentech


### 264P Progression-free survival (PFS) and site of first progression in HER2+ metastatic breast cancer (MBC) patients (pts) with (w) or without (w/o) brain metastases: A pooled analysis of tucatinib phase I studies

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**Background:** Brain metastases (BM) are frequent in HER2+ MBC occurring in > 30% of pts and are associated with significant neurologic morbidity and mortality. Current treatment strategies for BM primarily utilize radiation therapy (RT) and in selected instances surgical resection. Tucatinib is a highly selective oral HER2- tyrosine kinase inhibitor that has shown promising results in HER2+ MBC both in pts w and w/o BM.

**Methods:** Two Phase Ib studies of tucatinib were pooled to compare PFS and sites of relapse in pts w or w/o BM.

**Results:** 77 pts were analyzed, all treated at the recommended Phase 2 dose of 300mg PO BID of tucatinib, 50 in the 004 trial (tucatinib + T-DM1) and 27 in the 005 trial (tucatinib + trastuzumab + capcitabine). All pts were heavily pretreated w a median of 3 prior therapies including a taxane, trastuzumab, pertuzumab, T-DM1 and lapatinib. Four cohorts of pts were identified: 46% (35) had systemic metastases only, 17% (13) had previously treated (RT w or w/o surgery) and stable BM, 19% (15) had previously treated and progressive BM and 17% (13) had asymptomatic untreated BM demonstrated by screening MRI. Median PFS across cohorts was 8.5, 6.1, 9.0 and 7.1 months, respectively. No statistically significant difference in PFS was seen when comparing the non-BM cohort to all BM cohorts (median of 28.9 months, p = 0.65).

The risk of progression in brain w baseline BM was 48.8% overall (41.5% in brain only; 7.3% in brain and body) compared to an 11.1% overall (8.3% in brain only; 2.8% in brain and body) in pts w/o baseline BM.

**Conclusions:** 54% of pts entered tucatinib studies w baseline BM, either previously treated (stable or progressive) or untreated. The cohorts of pts analyzed appeared to differ only in the site of disease progression. Although pts w baseline BM primarily have progression in extraneural sites and pts w baseline BM primarily have progression in the CNS, PFS is comparable across cohorts. Furthermore, pts both w and w/o BM have durable responses w these combination therapies following multiple lines of prior HER2 targeted therapy. These data support the use of tucatinib in both pts w and w/o BM in the accruing HER2CLIMB trial.

**Clinical trial identification:** ONT-380-004 and ONT-380-005

**Legal entity responsible for the study:** Cascadian Therapeutics, Inc.

**Funding:** Cascadian Therapeutics, Inc.

**Disclosure:** All authors have declared no conflicts of interest.
265P Survival of patients with aromatase inhibitors sensitive, HR+ HER2- metastatic breast cancer treated with a first-line endocrine therapy or chemotherapy in a multicenter national observational study

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Background: For HR+/HER2- metastatic breast cancer (mBC), international guidelines recommend the use of endocrine therapy (ET) as first-line (L1) treatment except in case of “visceral crisis” for which chemotherapy (CT) is advised. Few studies directly compare these two treatment options. In 2014, UNICANCER launched the ESME program to centralize real-world data in oncology. We sought to use this database to study this question.

Methods: All patients (pts) who initiated treatment for a newly diagnosed mBC between January 2008 and December 2014 in all 18 French Comprehensive Cancer Centers were included in the ESME mBC database. ESME Research program centralized and analyzed retrospective data collection. Primary endpoint of the present study was progression free survival (PFS1) and overall survival (OS) according to L1 treatment for aromatase inhibitors sensitive (AIS) HR+/HER2-mBC pts.

Results: 6265 pts out of 16703 in ESME, had AIS HR+/HER2- mBC. As L1 therapy, 2733 pts (43.6%) received ET alone, while 3532 received CT (56.4%). Among these 3532 pts, 2073 (58.7%) received ET as maintenance treatment after CT. A Cox multivariate analysis with significant prognostic variables identified a lower risk of death in the patients with L1 ET (HR = 0.839, 95% IC [0.772-0.911], p < 0.001). Patients receiving CT were younger (median age 56 vs 66.6, 0.001), more likely to have visceral metastasis (61.4% vs 41.1%, p < 0.001) and SBR II primary tumors (31.3% vs 18.8%, p < 0.001). Median PFS1 was 15.18 months for L1 ET (95% CI, 14.45-16.20 vs 12.38 months for L1 CT +/- hormone maintenance (95% CI, 11.89-13.14), p < 0.001. Median OS was 60.28 months for L1 ET (95% CI, 57.62-64.09 vs 49.64 months for L1 CT (95% CI, 47.31-51.64), p < 0.001.

Conclusions: The results show that despite guidelines, a majority of AIS HR+/HER2-mBC pts still received CT as first-line treatment in the past years. PFS1 and OS data do not suggest any advantage of this aggressive strategy over ET alone. Advanced statistical methods using the propensity score will be presented in order to control for potential selection bias.

Legal entity responsible for the study: UNICANCER

Funding: UNICANCER

Disclosure: All authors have declared no conflicts of interest.

266P Use of everolimus in advanced hormone receptor positive metastatic breast cancer in a multicenter national observational study

A. Lardy-Cleaud1, P. Cotu3, S. Franke1, O. Le Saul1, S. Chabaud1, D. Parent2, B. Pistillì2, A. Lardy-Cleaud1, A. Maillet2, C. Veyret2, T. Pep3, L. Uver1, S. Gau1, M. Ung1, E. Chamorey1, P. Aureau1, S. Guesnina1, P. Augereau1, G. Simon1, T. Bachelot17
1Biostatistics, Centre Léon Bénard, Lyon, France, 2Medical Oncology, Institut Curie, Paris, France, 3Medical Oncology, Centre Léon Bénard, Lyon, France, 4Medical Oncology, Institut Jean Godinot, Reims, France, 5Medical Oncology, Gustave Roussy, Villejuif, France, 6Medical Oncology, Institut Bergonie, Bordeaux, France, 7Medical Oncology, Centre Oscar Lambret, Lille, France, 8Medical Oncology, Centre Henri Beauguerel, Rouen, France, 9Medical Oncology, Météor, Montpellier, France, 10Medical Oncology, Institut Universitaire du Cancer de Toulouse, Toulouse, France, 11Pharmacy, Centre Antoine Lacassagne, Nice, France, 12Biostatistics, Centre Georges-François Leclerc, Dijon, France, 13H&O, UNICANCER, Paris, France, 14Medical Oncology, Centre Paul Papin, Angers, France, 15Département d’Oncologie médicale adulte, Centre Léon Bénard, Lyon, France

Background: The everolimus-exemestane combination has been included in the International guidelines for advanced HR+ breast cancer (mBC) since the results of the BOLERO-2 trial. Marketing authorization has been granted in France in July 2012. We evaluated the incidence and indication of everolimus (EVE) use before and after marketing authorization and reimbursement.

Methods: All patients who initiated a treatment for a newly diagnosed mBC between 01/2008 and 12/2015 in all 18 French Comprehensive Cancer Centers have been included in the real life ESME database, which collects retrospective data using a clinical trial-like methodology.

Results: The ESME program included a total of 16,703 patients of which 9,921 had HR+/HER2- mBC. Median age at metastatic diagnosis was 62.0 year (range 23-96). Visceral metastases were present in 60.3% of cases. Only 4123 patients (41.4%) received endocrine therapy alone as first-line therapy, and 60% were deemed endocrine-resistant. Overall, 1,217 (12.3%) pts have received EVE during therapy as of Dec 2015 (all lines). EVE was given as first-line therapy in 117 pts (10% of all EVE pts and 1.2% of pts receiving a first-line therapy). In 99/117 pts (83%) EVE was combined with exemestane. Before 2012, EVE was used within clinical trials. After 2012, use of EVE increased steadily. Percentages in the Table refer to the total of pts who received any kind of treatment during a given year of observation (eg 506 pts took EVE in 2015 out of 4435). Median duration of EVE use was 6.9 months (range 0-65) as first line treatment and 3.9 months (range 0-65) in pretreated patients. Patient population and causes of EVE cessation will be detailed at the meeting.

Table: 266P

<table>
<thead>
<tr>
<th>Year</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>4</td>
<td>7</td>
<td>13</td>
<td>11</td>
<td>133</td>
<td>391</td>
<td>493</td>
<td>506</td>
</tr>
<tr>
<td>%</td>
<td>0.20</td>
<td>0.22</td>
<td>0.30</td>
<td>0.21</td>
<td>2.3</td>
<td>6.6</td>
<td>8.6</td>
<td>11.41</td>
</tr>
</tbody>
</table>

Conclusions: In this very large French national and representative cohort of HR+/HER2- mBC, EVE use rose quickly as soon as marketed. EVE was mostly used in pre-treated mBC albeit in probably too advanced pts. These data underline the need for physician and patient education for oral therapy.

Legal entity responsible for the study: UNICANCER R&D

Funding: UNICANCER

Disclosure: All authors have declared no conflicts of interest.
A better understanding of the mTNBC pt subpopulation and optimal tx sequencing is warranted to improve tx strategies and prolong survival.

Legal entity responsible for the study: Genentech, Inc.

Funding: Genentech, Inc.

Disclosure: P. Bajaj, C. Reyes, A. Stein, P. Cortazar: Employee of Genentech, Inc. and owner of Roche stock. D. Latremouille-Viau, A. Guerin: Employee of Analysis Group, Inc., which has received consulting fees and research funding from Genentech, Inc. All other authors have declared no conflicts of interest.

Table: 267P Summary of results

<table>
<thead>
<tr>
<th>Study</th>
<th>Total No. of patients in trial (randomisation if not 1:1)</th>
<th>Observed median, months (arm A v B)</th>
<th>Retrospectively calculated sample size</th>
<th>Factor (x)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PFS</td>
<td>TTP</td>
<td>OS</td>
</tr>
<tr>
<td>Acland 2001</td>
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<td>–</td>
<td>6.3 v 8.7b</td>
<td>18.2 v 20.1</td>
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<tr>
<td>Jassem 2001</td>
<td>267 a</td>
<td>–</td>
<td>6.2 v 8.3b</td>
<td>18.3 v 23.3b</td>
</tr>
<tr>
<td>Ejkertsen 2004</td>
<td>387 a</td>
<td>8.2 v 10.1b</td>
<td>–</td>
<td>18.0 v 19.1</td>
</tr>
<tr>
<td>Bontenbal 2005</td>
<td>216</td>
<td>–</td>
<td>6.6 v 8.0b</td>
<td>16.2 v 22.6b</td>
</tr>
<tr>
<td>Feyer 2005</td>
<td>397 a</td>
<td>–</td>
<td>3.4 v 6.1b</td>
<td>11.6 v 19.1b</td>
</tr>
<tr>
<td>von Minckwitz 2005</td>
<td>364 a</td>
<td>–</td>
<td>6.7 v 8.2b</td>
<td>–</td>
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<tr>
<td>Pardiosa 2005</td>
<td>331 a</td>
<td>3.9 v 7.5b</td>
<td>–</td>
<td>15.6 v 18.3</td>
</tr>
<tr>
<td>Albin 2008</td>
<td>529</td>
<td>–</td>
<td>4.0 v 6.1b</td>
<td>15.8 v 18.6b</td>
</tr>
<tr>
<td>Gray 2009</td>
<td>722</td>
<td>5.8 v 11.3b</td>
<td>–</td>
<td>24.8 v 26.5</td>
</tr>
<tr>
<td>Sprano 2009</td>
<td>751</td>
<td>–</td>
<td>7.9 v 9.8b</td>
<td>20.6 v 20.5</td>
</tr>
<tr>
<td>Miles 2010</td>
<td>488 (1:1)</td>
<td>8.2 v 10.1b</td>
<td>–</td>
<td>31.9 v 30.2</td>
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<tr>
<td>Robert 2011</td>
<td>615 (1:2)</td>
<td>5.7 v 8.6b</td>
<td>–</td>
<td>22.8 v 25.7</td>
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<tr>
<td>Gilgorov 2014</td>
<td>185</td>
<td>4.3 v 11.9b</td>
<td>–</td>
<td>23.7 v 39.0b</td>
</tr>
<tr>
<td>Lorusso 2014</td>
<td>233</td>
<td>–</td>
<td>7.8 v 9.4c</td>
<td>28.0 v 30.1</td>
</tr>
</tbody>
</table>

*Duration of accrual and/or follow-up not reported; accrual period assumed to be 1/3 of study duration.

aStatistically significant.

Table: 268P

<table>
<thead>
<tr>
<th>1ª-line, N = 411</th>
<th>%</th>
<th>Median OS [95% CI], mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>-</td>
<td>16.7 [15.2; 18.0]</td>
</tr>
<tr>
<td>Single agent</td>
<td>45</td>
<td>15.6 [13.2; 18.6]</td>
</tr>
<tr>
<td>Combination</td>
<td>55</td>
<td>17.0 [15.1; 19.1]</td>
</tr>
<tr>
<td>Tx regimen</td>
<td>22</td>
<td>–</td>
</tr>
<tr>
<td>Single agent taxane (docetaxel/ paclitaxel (pact)/ nab-pact)</td>
<td>14</td>
<td>–</td>
</tr>
<tr>
<td>Anthracylcline (ATC; doxorubicin [Dox]/epirubi- cin/liposomal Dox) + cyclophosphamide +/- taxane</td>
<td>13</td>
<td>–</td>
</tr>
<tr>
<td>Platinum (carboplatin/cisplatin/oxaliplatin) + taxane</td>
<td>13</td>
<td>–</td>
</tr>
<tr>
<td>Bevacizumab-containing</td>
<td>10</td>
<td>–</td>
</tr>
<tr>
<td>Gemcitabine (Gem) + platinum</td>
<td>10</td>
<td>–</td>
</tr>
<tr>
<td>Cap</td>
<td>9</td>
<td>–</td>
</tr>
<tr>
<td>Other</td>
<td>21</td>
<td>–</td>
</tr>
<tr>
<td>2ª-line, N = 298</td>
<td>-</td>
<td>14.2 [10.5; 22.3]</td>
</tr>
<tr>
<td>Single agent</td>
<td>72</td>
<td>12.9 [10.5; 22.3]</td>
</tr>
<tr>
<td>Combination</td>
<td>28</td>
<td>16.2 [8.1; -]</td>
</tr>
</tbody>
</table>

Annals of Oncology abstracts

Volume 28 | Supplement 5 | September 2017
doi:10.1093/annonc/mdx365 | 87
Background: Systemic treatment outcomes for advanced triple-negative breast cancer (aTNBC) are worse compared to other disease subtypes, due to aggressive behaviour, heterogeneity and lack of molecular targets. Many options are under investigation although most patients receive standard cytotoxic chemotherapy. We aimed to provide better insight into the efficacy of different lines of therapy for aTNBC (overall response rate [ORR], median progression-free survival [mPFS] and median overall survival [mOS]) to better inform discussion with patients, decision-making and referral for clinical trials.

Methods: We retrospectively identified 268 patients diagnosed with aTNBC from 01/12/2011 to 30/11/2016 from our electronic records. Patients' and tumour characteristics were recorded, along with systemic treatment outcomes. Chi-squared/Fishers exact test and Kaplan-Meier statistical methods were utilised.

Results: 186 patients treated with ≥1 line of palliative systemic treatment were eligible for the analysis with a median age at 55 (range 26-91), 53.8% had ECOG Performance Status 0 and 69.9% visceral involvement. 38.6% had a disease-free interval (DFI) ≤ 12 months following surgery and 13.4% had de novo advanced disease, 11.4% carried a BRCA mutation. 64.5% received 2 lines of therapy, 37.6% had 3 and 21.5% had 4. ORR and mPFS to first line therapy were respectively 43.9% (95% CI 36.5-51.5) and 3.7 months (95% CI 2.9-5.1), to second line was 40.2% (95% CI 31.2-49.6) and 3.5 months (95% CI 2.9-4.1) and to fourth line was 25.0% (95% CI 12.7-41.2) and 2.1 months (95% CI 1.6-2.8).

First line patients with a DFI >12 months had ORR of 47.7% (95% CI 36.8-58.7) compared to 35.8% (95% CI 23.1-50.2) for those with a DFI <12 months (p = 0.172). mPFS was respectively 5.2 months (95% CI 3.4-6.5) compared to 2.7 (95% CI 1.8-3.6) (p = 0.005).

Table: 269P Demographics at advanced stage disease diagnosis

<table>
<thead>
<tr>
<th>Age group N (%)</th>
<th>Median age 55 (range: 26-91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 60 years</td>
<td>117 (62.9)</td>
</tr>
<tr>
<td>≥ 60 years</td>
<td>100 (53.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ECOG Performance Status N (%)</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 (53.8)</td>
<td>75 (40.3)</td>
<td>11 (5.9)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease sites N (%)</th>
<th>Visceral</th>
<th>Non-visceral only</th>
<th>Invasive ductal</th>
<th>Invasive lobular</th>
<th>Mixed</th>
<th>Metaplastic</th>
<th>Other</th>
<th>Not available</th>
</tr>
</thead>
<tbody>
<tr>
<td>130 (69.9)</td>
<td>56 (30.1)</td>
<td>112 (60.2)</td>
<td>7 (3.8)</td>
<td>2 (1.1)</td>
<td>3 (1.6)</td>
<td>2 (1.1)</td>
<td>60 (33.2)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>De novo advanced disease N (%)</th>
<th>25 (13.4%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>186 (100)</td>
</tr>
<tr>
<td>2</td>
<td>120 (64.5)</td>
</tr>
<tr>
<td>3</td>
<td>70 (37.6)</td>
</tr>
<tr>
<td>4</td>
<td>40 (21.5)</td>
</tr>
<tr>
<td>5</td>
<td>20 (10.7)</td>
</tr>
<tr>
<td>6</td>
<td>5 (2.7)</td>
</tr>
<tr>
<td>7</td>
<td>1 (0.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DFI N (%)</th>
<th>Median PFS 33 months [95%CI 27.4-39.7]</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 12 months</td>
<td>56 (38.6)</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>89 (61.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BRCA</th>
<th>Wild-type</th>
<th>Mutated</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>66 (35.7)</td>
<td>21 (11.4)</td>
<td>98 (53.0)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: The response rates observed in this population of patients are similar to those observed in published clinical trials. However, the PFS rates are short, and as a result early consideration for inclusion in clinical trials of novel approaches can be justified in these patients.

Legal entity responsible for the study: Nicolet Matteo, Luca Battisti
Funding: None
Disclosure: All authors have declared no conflicts of interest.

270P

Unprotected hormone receptor positive/HER2-negative metastatic breast cancer survival with front-line chemotherapy and maintenance endocrine therapy

B Sabatier1, A. Meskine, M.A. Cappiello, J.-M. Extra, C. Tarpin, F. Rousseau, M. Provansal, F. Bertucci, P. Viens, A. Gonçalves

Medical Oncology, Institut Paoli-Calmettes, Marseille, France

Background: Except some life threatening cases, combination of endocrine therapy and CDK4/6 inhibitors is becoming the standard first line treatment for women with hormone receptor (HR) positive/HER2 negative advanced and metastatic breast cancer (MBC). However cost-effectiveness analyses are lacking concerning this therapy. As chemotherapy also targets cell cycle we wondered how sequential combination of chemotherapy and maintenance endocrine therapy could be effective as first line treatment for naive HR+/-HER2- MBC.

Methods: We retrospectively collected from our institutional database (“Institut Paoli-Calmettes”, Marseille, France) cases of metastatic breast cancer treated with chemotherapy plus maintenance endocrine therapy as first line treatment between January 2000 and December 2015. Progression-free survival (PFS) and Overall Survival (OS) were analyzed using the Kaplan-Meier’s method. We also conducted univariate (UV) and multivariate analyzes including menopausal status, visceral disease, pathological subtype, and progesterone receptor expression assessed by immunohistochemistry.

Results: A total of 183 female patients were included with a median age at diagnostic of 56.9 years. Most of them were postmenopausal (n = 114, 65.9%) and 108 (59.7%) had visceral metastases. Anthracyclines-Taxanes combinations were used for 162 patients (88.5%). Median number of chemotherapy cycles was 6. Endocrine therapy was aromatase inhibitors and tamoxifen for 120 (67.8%) and 56 (31.6%) cases, respectively. Median PFS was 33 months [95CI = 25-38] and median OS was 79 months [95CI = 63-101]. In UV analysis pre-menopausal status (HR= 0.58), non-ductal non-lobular subtype (HR=0.47), and absence of visceral disease (HR= 0.31) were correlated to better OS. All these features remained significant in multivariate analysis. We observed no death related to treatment.

Conclusions: Following these results, and with the issues of cost-effectiveness related to newly approved therapies, first-line chemotherapy plus maintenance endocrine therapy might be considered for untreated HR+/-HER2- MBC.

Legal entity responsible for the study: Institut Paoli-Calmettes
Funding: None
Disclosure: R. Sabatier: Travel grants: Pfizer. Consultant: Novartis, Pfizer. Investigator in clinical trials promoted by Novartis and Lilly. F. Bertucci: Investigator in clinical trials promoted by Novartis and Lilly. A. Gonçalves: Consultant: Novartis. Investigator in clinical trials promoted by Novartis and Lilly. All other authors have declared no conflicts of interest.

271P

Can we predict subsequent brain metastasis in patients with metastatic breast cancer?

S.E. El Zawawy

Clinical Oncology, University of Alexandria Faculty of Medicine, Alexandria, Egypt

Background: The one year overall survival of breast cancer patients with brain metastasis is only 20%–40%. Approximately, 80% of brain metastases occur after the diagnosis of other systemic metastatic lesions. Due to this dismal prognosis, prophylactic approaches as cranial irradiation, high-dose methotrexate, or lapatinib could be evaluated as preventative measures. However, these approaches are usually toxic and cannot be applied to all patients. This study is carried out to evaluate risk factors that have an impact on subsequent development of brain metastasis in metastatic breast cancer patients and thus, those patients can be candidates for prophylactic measures.

Methods: The medical records of 267 metastatic breast cancer patients were retrospectively reviewed for demographic, clinic pathological, metastatic and treatment characteristics.

Results: 46 out of 267 patients developed brain metastasis with an incidence of 17.2%. Significant risks include age <40y 28.7% patients compared to1.6% for age 40–50y and 11.1% for age ≥50y (P = 0.031) and 24.2% premenopausal patients compared to 11.4% for postmenopausal (P = 0.013), Her2/neu overexpression (48.5%) and triple negative (35.3%) compared to 11.3% patients with ER positive (P = 0.0001, 0.003), high grade compared to low grade tumors (33.6% vs 12.6% P = 0.005). Patients with N2, 3 had higher risk than N0, 1 (44% vs 13.8%) (P = 0.01), 30.9% patients with disease free duration (DFD) < 2 years developed brain metastasis compared to 22.1% for M1 patients and 11.1% patients with DFD >2years (P = 0.019, 0.053). 3.6% patients with bone only metastasis developed brain metastasis compared to 20.6% patients with visceral only metastasis and 27.4% patients with bone and visceral metastasis (P = 0.036, 0.014). 32.3% patients with lung containing metastasis developed brain metastasis.
comparing patients with and without metastatic lesions. The median follow-up period was 6.4 years (0.2–12). 2
patients were diagnosed with BM and were treated with palliative CT only. The median follow-up period was 6.4 years (0.2–12). 2
and 5-year OS and PFS were respectively 90.8% and 52.1% and 45.7% and 21.4%. Significant
predictors for better OS (p
5 0.001) were age at diagnosis to death or last follow up. Cox proportional models were used to calculate
Hazard Ratio and 95% Confidence Intervals (CI). Performances of breast-GPA and modified breast-GPA were compared using Harrell’s concordance index.

Results: At last follow-up, 632 patients (94.6%) had died. Median OS was 8.1 months (95% CI 6.9–9.4 months). Median age at BM diagnosis was 56 years (range 24–85).

Tumor phenotype distribution was: triple negative (20.1%), hormone receptor (HR)-
positive (21.6%), HER2+ (20.4%) and HR−HER2+ (33.4%). KPS distribution
was: 90–100 (19.6%), 70–80 (49.0%), 60 (12.8%) and 50 (18.6%). 355 patients
(33.5%) had >3 BM. Number of BM (1,2,3,
4) was significantly associated with OS (p < 0.001). Both breast-GPA and modified breast-GPA predicted OS (p < 0.001).

Conclusions: Number of BM is a significant prognostic factor in BC patients with BM and modified breast-GPA performs better than breast-GPA in predicting prognosis of these patients.

Legal entity responsible for the study: Department of Surgery, Oncology and Gastroenterology, University of Padova, Padua, Italy

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Table: 273P

<table>
<thead>
<tr>
<th>Breast GPA category</th>
<th>Number of patients (%)</th>
<th>Median OS, months (95% CI)</th>
<th>Hazard Ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5-4</td>
<td>86 (13.5%)</td>
<td>18.8 (14.5-22.6)</td>
<td>ref</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2.5-3</td>
<td>248 (38.8%)</td>
<td>10.3 (8.8-11.8)</td>
<td>1.45 (1.12-1.88)</td>
<td></td>
</tr>
<tr>
<td>1.5-2</td>
<td>194 (30.4%)</td>
<td>6.2 (4.9-7.6)</td>
<td>2.04 (1.56-2.66)</td>
<td></td>
</tr>
<tr>
<td>0-1.0</td>
<td>111 (17.4%)</td>
<td>2.5 (1.8-3.2)</td>
<td>4.97 (3.67-6.71)</td>
<td></td>
</tr>
</tbody>
</table>

Modified breast GPA category

<table>
<thead>
<tr>
<th>Number of patients (%)</th>
<th>Median OS, months (95% CI)</th>
<th>Hazard Ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5-4</td>
<td>37 (5.8%)</td>
<td>18.9 (17.2-20.5)</td>
<td>ref</td>
</tr>
<tr>
<td>2.5-3</td>
<td>209 (32.8%)</td>
<td>15.2 (12.1-18.3)</td>
<td>1.43 (0.96-2.09)</td>
</tr>
<tr>
<td>1.5-2</td>
<td>257 (40.3%)</td>
<td>7.9 (5.9-9.9)</td>
<td>2.30 (1.59-3.33)</td>
</tr>
<tr>
<td>0-1.0</td>
<td>135 (21.2%)</td>
<td>2.3 (1.9-2.8)</td>
<td>7.03 (4.72-10.46)</td>
</tr>
</tbody>
</table>
Background: The addition of pertuzumab (P) to trastuzumab (H) and docetaxel improves survival in clinical trials of patients with HER2+ MBC, and is a guideline-recommended standard of care for this population. In the real-world, however, various factors may influence treatment decisions. Systematic Therapies for HER2-positive Metastatic Breast Cancer Study (SystHERs) is a fully enrolled (June 2012–June 2016), ongoing, US-based, observational study that captures real-world data for patients with MBC. Here, we describe the baseline characteristics and treatment patterns of patients who received 1L PH or H without P.

Methods: Eligible patients had HER2+ MBC diagnosed within 6 months of enrollment and were ≥18 years of age. Patients were compared descriptively by 1L treatment (PH vs H without P), defined as any therapy received up to first progression.

Results: As of February 10, 2017, among 978 eligible patients, 949 had received 1L treatment. PH, n = 711; H without P, n = 174; no H, n = 64) (Table). Of patients in the PH and H without P cohorts, respectively, remain on study. Median follow-up from 1L treatment start was 22 and 25 months, respectively. In patients treated with PH, median duration of treatment with H and P were 15 and 13 months, respectively. In the H without P cohort, median duration of H was 15 months. Among all patients, 68% (648/949) received PH + taxane.

Conclusions: Of patients with HER2+ MBC in the real-world SystHERs study, 68% were treated with PH + taxane. Compared with patients who received PH, those who received H without P were older, less commonly had liver metastasis, and more commonly had prior cardiovascular disease, suggesting that these characteristics may have influenced the treatment choice between PH vs H without P.

Clinical trial identification: NCT01615068

Legal entity responsible for the study: Genentech/Roche

Table: 274P

<table>
<thead>
<tr>
<th>PH (n = 711)</th>
<th>H without P (n = 174)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at MBC diagnosis, years (range)</td>
<td>55 (21–89)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>565 (79)</td>
</tr>
<tr>
<td>Eastern Cooperative Oncology Group performance score 0–1, n (%)</td>
<td>613 (86)</td>
</tr>
<tr>
<td>Urban or suburban living location, n (%)</td>
<td>565 (78)</td>
</tr>
<tr>
<td>De novo, n (%)</td>
<td>379 (53)</td>
</tr>
<tr>
<td>Estrogen receptor positive and/or progesterone receptor positive, n (%)</td>
<td>496 (70)</td>
</tr>
<tr>
<td>Visceral, n (%)</td>
<td>476 (67)</td>
</tr>
<tr>
<td>&gt;3 metastatic sites, n (%)</td>
<td>232 (33)</td>
</tr>
<tr>
<td>Liver metastasis, n (%)</td>
<td>300 (42)</td>
</tr>
<tr>
<td>Central nervous system (CNS) metastasis, n (%)</td>
<td>45 (6)*</td>
</tr>
<tr>
<td>Prior cardiovascular disease, n (%)</td>
<td>80 (11)</td>
</tr>
<tr>
<td>Treatment for early breast cancer, n (%) Any adjuvant or adjuvant therapy Any H</td>
<td>n = 532 293 (88) 187 (56)</td>
</tr>
</tbody>
</table>

1L treatment patterns, n (%) (Treatments are not mutually exclusive)

With chemotherapy TAxane Docetaxel Paclitaxel Platinum

| 673 (95) 648 (91) 479 (67) | 117 (67) 87 (50) |
| 195 (27) 69 (10) | 34 (20) 51 (29) 40 (23) |

With hormonal therapy Aromatase inhibitor Tamoxifen

| 282 (40) 221 (31) 61 (9) | 94 (54) 76 (44) 14 (8) |

*In patients who did not receive H, 25% (16/64) had CNS metastasis.

**In patients with recurrent disease.
examine baseline characteristics, first-line treatments, and breast cancer–specific survival (BCSS) by age.

Methods: SystHEIRs is a fully enrolled [Jun 2012–Jun 2016], ongoing, US-based, observational study. Pts were ≥18 years old and had HER2þ MBC diagnosed within 6 months of enrollment. Pts were grouped by age at MBC diagnosis (<50, 50–69, or ≥70 years) and compared descriptively. BCSS was defined as time from the date of MBC diagnosis to date of death due to MBC progression.

Results: As of Feb 10, 2017, of 978 eligible pts, 287 were <50 years old, 563 were 50–69, and 128 were ≥70 at MBC diagnosis. Median follow-up from MBC diagnosis was 23, 18, and 19 months, respectively. Baseline characteristics, first-line treatments, and BCSS are shown (Table). In pts who received chemotherapy, docetaxel was the most common agent in pts <50 (67%) and 50–69 (64%) followed by paclitaxel (29% in both groups), whereas in pts ≥70, 63% and 45% received docetaxel and paclitaxel, respectively.

Conclusions: In this preliminary real-world analysis of pts with HER2þ-MBC, pertuzumab (P) þ trastuzumab (H) was more commonly used than H without P across all age groups. Pts <50 and 50–69 years old more commonly received PH þ taxane than those ≥70 (72% and 69% vs 43%, respectively). Compared with younger pts, those ≥70 received regimens with chemotherapy less commonly (89% and 87% vs 67%), and more commonly received regimens with H without P (13% and 17% vs 54%) or hormonal therapy (39% and 41% vs 52%). Pts <50 had longer BCSS than those ≥70 (78% vs 64% at 3 years).

Clinical trial identification: NCT01655068

Legal entity responsible for the study: Genentech/Roche

Funding: Genentech/Roche


276P Defining priorities for research: Interim results of the Canadian metastatic breast cancer priority setting partnership

N. Nixon1, S. Verma1, C. Simmons2, I. Lemieux3

1Medical Oncology, Tom Baker Cancer Centre, Calgary, AB, Canada, 2Medical Oncology, British Columbia Cancer Agency, Vancouver, BC, Canada, 3Medical Oncology, CHU De Quebec, Quebec, QC, Canada

Background: Research priorities are generally determined by funders and researchers without direct involvement and input from patients and caregivers. Certain disease areas have incorporated the patient voice to determine patient driven priorities. In this study, this approach was employed to better understand the needs and priorities of metastatic breast cancer patients and their caregivers.

Methods: This study was conducted using methodology outlined by the James Lind Alliance. A steering committee of patients, physicians, patient advocates, and allied health care professionals was assembled to oversee the research study. The initial survey collected unanswered research questions from patients, caregivers, and clinicians. Responses were collected and categorized by members of the steering committee. Here we present the results from the national survey.

Results: Between November 2016 and April 2017, 733 responses from 311 individuals were collected (62% patients, 11% physicians, 9% caregivers or relatives, 5% nurses/ allied health professionals, 2% patient organization representatives, and 10% other). The main themes for key patient priorities are: 136 (19%) related to treatment and monitoring, 78 (11%) linked lifestyle and alternative therapy, 58 (8%) regarded tumour biology, 53 (7%) regarded psychosocial aspects, 46 (6%) to diagnosis, 35 (5%) to toxicity, 24 (3%) to prevention, and 17 (2%) to young or pre-menopausal population. Two hundred and eighty-six (39%) were considered out of scope. The most frequently identified priorities included the role of alternative therapies for improving survival, the role of immune therapy for treating metastatic breast cancer, and the potential for improving outcomes with early detection/surveillance with modern treatment and diagnostic modalities.

Conclusions: Patient derived research priorities in advanced breast cancer point to an improved understanding of alternative therapies, integration of immune therapy and a focus on early detection of relapse. These priorities should be addressed by the research community to meet the needs of our patients with advanced breast cancer.

Legal entity responsible for the study: Nancy Nixon

Funding: None

Disclosure: S. Verma: Advisory Boards for: Roche, Pfizer, Novartis, Eli Lilly, Merck, Amgen. All other authors have declared no conflicts of interest.
Breast cancer (BC) is the most common cancer in India with 150000 new cases are diagnosed and 70000 women dies of it every year. Triple-negative breast cancer (TNBC) is an aggressive subtype that lack ER and PR expression and absence of overexpression of amplified HER2. TNBC accounts for 15%-25% of all invasive BC, occurs more in younger women and is associated with higher histologic grade and advanced disease. Our goal was to study the relation between triple-negative receptor status and major determinants of clinical outcome, such as response to neoadjuvant chemotherapy (rate of pathologic complete response [pCR]), progression free survival (PFS), site-specific distribution of recurrence, postrecurrence survival (PRS) and overall survival (OS). Methods: We included 2658 patients who received neoadjuvant chemotherapy at Jawaharlal Nehru Cancer Hospital Bhopal for stage I-III breast cancer from 1990 to 2010 and for whom complete receptor information were available. Clinical and pathologic parameters, pCR, survival measurements and organ-specific relapse rates were compared between patients with TNBC and non-TNBC. Results: 505 patients (19%) had TNBC. Mean age for TNBC (42 years) was lesser than non-TNBC (56 years; P < .002). Patients with TNBC had significantly higher pCR rates (34% vs 14%; P < .008) but decreased 5 year PFS rates (P < .0001) and 5 year OS rates (P < .0001). TNBC was associated with increased risk for distant metastases (P < .0005), lower risk for bone recurrence (P = .004) and shorter PFS (P < .0001). Recurrence and death rates were higher for TNBC only in the first 5 years. If pCR was achieved, patients with TNBC and non-TNBC had similar survival (P = .36). Patients with residual disease (RD) had worse OS if they had TNBC compared with non-TNBC (P < .0001). Conclusions: TNBC patients have increased pCR rates (excellent survival) compared with non-TNBC. However TNBC patients with RD have significantly worse survival after neoadjuvant chemotherapy in first 5 years. TNBC patients may be best treated with 3rd generation adjuvant or neoadjuvant chemotherapy regimens that achieve the highest possible pCR rates. With high risk of distant metastases, these patients require closer surveillance in initial years of follow-up. 

Clinical trial identification: IND16434A

Disclosure: All authors have declared no conflicts of interest.

Funding: None. Legal entity responsible for the study: Jawaharlal Nehru Cancer Hospital, Bhopal, India. 

Annals of Oncology
assess overall survival (OS) of younger MBC pts compared to older ones, and to explore 1st trt choices in a large real-life multicenter cohort.

**Methods:** The Epidemiological Strategy and Medical Economics (ESME) Research program aims to collect high-quality real-world data in oncology from 18 French Comprehensive Cancer Centers. Pts who started treatment for a newly diagnosed MBC between Jan 2008 and Dec 2014 were selected in the ESME database. The primary end point of the FICHE-Young study was to compare adjusted OS in pts diagnosed with endocrine-sensitive HR+/HER2- MBC and aged ≤45 vs > 45 at diagnosis. We also evaluated 1st trt choices in both categories and its correlation with OS. Analyses will be adjusted on a propensity score, in order to control selection biases associated with non-randomization.

**Results:** 6265 pts out of 16703 in ESME had HR+/HER2- MBC. Characteristics and 1st trt choices are listed in the Table. Median OS was 62.3 months (mos) (95% CI 56.5-69) in pts ≤45 and 52.8 mos in those >45 (95% CI 50.7-55), p<0.001. In pts ≤45, we did not show any statistically significant difference in OS between first line ET and CT+/ET (68.3 mos for ET (95% CI, 56.8-NE) vs 59.0 mos for CT+/ET) (95% CI, 55.9-69, p = 0.328).

**Conclusions:** With the limitations of a non-randomized study population, in this real-world setting, younger HR+ MBC pts did not show a poorer prognosis compared to older patients. Many young pts received CT as first line treatment, with no demonstrated benefit over ET alone.

**Legal entity responsible for the study:** UNICANCER

**Funding:** UNICANCER

**Disclosure:** All authors have declared no conflicts of interest.

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**Table: 280P**

<table>
<thead>
<tr>
<th></th>
<th>≤ 45 yrs old</th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>851</td>
<td>5414</td>
</tr>
<tr>
<td>Median age</td>
<td>40.0 [23.44]</td>
<td>63 [45.95]</td>
</tr>
<tr>
<td>Visceral metastases</td>
<td>56.3%</td>
<td>51.6%</td>
</tr>
<tr>
<td>De novo MBC</td>
<td>41%</td>
<td>42.4%</td>
</tr>
<tr>
<td>Median time to onset of MBC 1st trt: ET alone</td>
<td>3.28 yrs [0.50;19.53]</td>
<td>9.18 yrs [0.50;43.02]</td>
</tr>
<tr>
<td>Chemo +/- maintenance ET</td>
<td>19.4%</td>
<td>47.4%</td>
</tr>
<tr>
<td>Chemo +/- maintenance ET</td>
<td>80.6%</td>
<td>52.6%</td>
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</table>

---

**281P Cell-free circulating DNA as independent prognostic markers in metastatic breast cancer**

**J. Cheng,1 H. Surawy,1 M. Wallwever,1 T. Holland-Leitz,2 K. Cuk,3 S. Scionti,4 A. Trumpp4, K. Pantel5, C. Sohn2, A. Schneeweiss6, B. Burwinkel1**

1Division of Molecular Epidemiology, German Cancer Research Center, Heidelberg, Germany; 2Department of Gynecology and Obstetrics, Women’s University Hospital, University of Heidelberg, Heidelberg, Germany; 3Department of Biostatistics, German Cancer Research Center, Heidelberg, Germany; 4Division of Stem Cells and Cancer, German Cancer Research Center, Heidelberg, Germany; 5University Hospital Hospital-Hamburg-Eppendorf, Department of Tumor Biology, Hamburg, Germany; 6Division Gynecologic Oncology, National Center for Tumor Diseases (NCT) University Hospital, Heidelberg, Germany.

**Background:** Blood-based biomarkers like microRNAs, cell-free DNA and circulating tumor cell hold great promise as they are reproducible and easily accessible in cancer patients. Cell-free DNA variables, such as cell-free DNA concentrations (cfDNA conc) and cell-free DNA integrity (cfDI), have great potential as diagnostic and prognostic markers in breast cancer patients. Here we investigated the potential prognostic ability of cfDNA conc and cfDI in a prospective study cohort of metastatic breast cancer (MBC) patients.

**Methods:** Blood was collected for cfDNA extraction from patients when enrolled about to start the first cycle of systematic therapy at baseline (MBCLB), and after the first cycle of systematic therapy (MBCC1). cfDNA conc and cfDI in blood plasma were evaluated by measuring the short and long fragments of two repetitive DNA elements, ALU and LINE1. We detected 32 gene amplifications, with MYC being the most common (n = 5, 15.6%), andamageability. We did not see any difference in overall survival between patients after one cycle of therapy with odds ratio (OR) and 95% confidence interval (CI) of 0.70 (0.48 - 1.01) for ALU cfDI, 0.63 (0.44 - 0.92) for LINE1 cfDI, 2.44 (1.68 - 3.53) for ALU cfDNA conc, 2.12 (1.47 - 3.06) for LINE1 cfDNA conc for overall survival. When four cfDNA variables were combined, it can reach an OR of 2.53 (1.77-3.62) for overall survival analysis of patients.

**Conclusions:** In summary, we observed a decreased cfDNA conc and increased cfDI from the enrollment of the study to the first cycle of systematic therapy in MBC patients. cfDNA conc and cfDI can serve as independent prognostic markers in MBC patients after the first cycle of systematic therapy.

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**Legal entity responsible for the study:** Molecular Biology of Breast Cancer, Department of Gynecology and Obstetrics, University of Heidelberg, Heidelberg, Germany

**Funding:** The University Hospital of Heidelberg, Heidelberg, Germany; the German Cancer Research Center (DKFZ), Heidelberg, Germany

**Disclosure:** All authors have declared no conflicts of interest.
Neutrophil-lymphocyte ratio (NLR) might be a surrogate marker of the tumor microenvironment and has been proposed as a prognostic factor for different tumors. A meta-analysis of NLR for breast cancer (BC) showed that higher values at diagnosis were associated with lower survival. However, these results were mainly derived from the analysis of early BC cases: only three of twelve articles included women with metastatic breast cancer (MBC), sample size was small and no differential statistical analysis was performed for MBC. The aim of this work was to determine the prognostic value of NLR for MBC.

**Methods:** We retrospectively collected clinical and analytical data from a series of consecutive MBC patients treated in one center between 2009 and 2016. NLR (neutrophil count/lymphocyte count) was obtained from differential white blood cell count at diagnosis of metastasis, before starting any treatment. Non-parametric tests (Mann Whitney U, Kruskal-Wallis) were used to evaluate differences of NLR between groups.

**Results:** 265 consecutive patients with MBC were included, 117 of them (44%) with metastatic disease at diagnosis. Median age: 59 (19-95); ECOG 0-1 (69%), 2-3 (12%); site: bone only (37%), visceral only (18%), bone + visceral (30%); tumor subtype: HR (hormone receptor) +/HER2- (59%), HR-/HER2+ (17%), HR-/HER2- (14%); disease free interval in recurrent MBC: <24 months (48, 32%), > 24 months (100, 67%). Outcomes: 135 deaths; median overall survival (OS): 35 months (95%CI: 27.4-42.6). Median NLR was 2.31 (range: 0.70-44.33), with significant higher values in women with ECOG 2-3 (p = 0.008) or negative estrogen receptors (p = 0.03). Univariate Cox model of OS showed a HR = 1.07 (95%: 1.03-1.11; p = 0.001) for NLR as a continuous variable; using the median value as cut-off, HR = 1.74 (95%CI: 1.05-2.87; p = 0.024). A multivariate Cox model showed the independent value of NLR for OS (Table).

**Conclusions:** A higher NLR at diagnosis is a negative prognostic factor for overall survival in metastatic breast cancer. These data, if prospectively validated, may lead to differential therapeutic survival in metastatic breast cancer. These data, if prospectively validated, may support the addition of NLR to MBC prognostic models and may lead to differential therapeutic approaches in patients with higher NLR.

**Legal entity responsible for the study:** Francisco Ayala de la Peña

**Funding:** None

**Disclosure:** All authors have declared no conflicts of interest.

Results: Best therapeutic efficacies of DNA destabilizers with angiogenesis inhibitors in combination than monotherapy with either (OR: 5.011-7.286; p value < 0.001) indicated a significant prevalence of basal like TNBCs in populations. Statistical significance with antimetabolites as combination therapy (OR: 2.343) p value: 0.018 and not with microtubule stabilizer (OR: 0.377) were remarkable, indicating probability of less predominance of M or MSL type TNBC in a population. PARP inhibitors or T cell targeted therapies were also found promising (OR: 1.120, 1.400 respectively), warranting their targeted usage for BCRC deficient and IM type TNBCs respectively.

Conclusions: For TNBC treatment, personalized medicine and not a generalized treatment strategy should be considered.

Legal entity responsible for the study: Netaji Subhas Chandra Bose Cancer Research Institute

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Table: 288P

<table>
<thead>
<tr>
<th>Type of post-ILRR relapse</th>
<th>Local recurrence</th>
<th>Locoregional recurrence</th>
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</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>Loco-regional</td>
<td>117 (13%)</td>
<td>57 (12%)</td>
</tr>
<tr>
<td>Distant</td>
<td>438 (49%)</td>
<td>305 (64%)</td>
</tr>
<tr>
<td>Loco-regional + distant</td>
<td>13 (1%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Death</td>
<td>335 (37%)</td>
<td>111 (23%)</td>
</tr>
<tr>
<td>Total</td>
<td>903 (100%)</td>
<td>476 (100%)</td>
</tr>
</tbody>
</table>

Conclusions: Survival after LRR has gradually improved over the last 35 years regardless of other recognized prognostic factors.

Legal entity responsible for the study: Karolinska Institute

Funding: Dagmar Fersbinnesfond

Disclosure: All authors have declared no conflicts of interest.

288P Neutrophil-to-lymphocyte ratio in metastatic breast cancer: Association with clinicopathological features and outcome

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Background: Tumors are closely linked with systemic inflammation, of which neutrophil-to-lymphocyte ratio (NLR) represents a simple and inexpensive tool of investigation. Previous data suggested that a high NLR is associated with poor prognosis in several breast cancer (BC) subtypes. However, few studies involved patients (pts) with metastatic breast cancer (MBC).

Methods: We retrospectively analyzed clinicopathological features and treatment outcome of 595 consecutive mBC pts treated at the Department of Oncology of Udine, Italy, between 2004 and 2014. NLR was calculated from the blood count performed before first-line therapy start. Differences in NLR according to clinicopathological characteristics were investigated through chi-square test. Cox regression was used to determine the prognostic impact of NLR.

Results: A statistically significant higher NLR was found in pts whose tumor had the following features: high grade (P < 0.005), ductal isotype (P = 0.02), ER negativity (P < 0.0001), high Ki-67 (P < 0.05). There were no statistical differences in NLR between HER2-positive and HER2-negative BC (P = 0.33). Among subtypes, triple-negative BC were associated with higher NLR, while luminal HER2+ BC with lower NLR (P = 0.084). No statistical differences in NLR were found according to visceral disease (P = 0.13) nor according with bone-only disease (P = 0.24). At univariate analysis, a NLR > 2.64 was associated with worse progression-free survival after first line therapy (HR 1.41, 95% CI 1.11-1.79, P = 0.005) and with worse overall survival (HR 1.76, 95% CI 1.32-2.36, P < 0.0001). The statistical significance was lost at multivariate analysis (P = 0.08 and P = 0.13, respectively). Of note, a subgroup analysis showed a significant prognostic value of NLR in HER2-positive subtype (HR 4.89, 95% CI 1.33-21.23).

Conclusions: High NLR was associated with pathological features of BC, but did not represent an independent prognostic factor at multivariate analysis. Further investigation is warranted to identify the appropriate cut-off value of NLR and the BC subtypes in which its prognostic role could be more useful.

Legal entity responsible for the study: University of Udine

Funding: None

Disclosure: All authors have declared no conflicts of interest.

288P Prognosis after loco-regional recurrence of breast cancer: 35 years longitudinal data from the Stockholm cancer register

C. Falato1, J. Eriksson1, A. Sofadi1, S.K. Taylor2, A. Nordblom1, J. Fredriksson1, J. Harnon1, J. Bergh1, T. Foukalas1

1Oncology and Pathology, Karolinska University Hospital-Solna, Stockholm, Sweden, 2Dept of Medical Oncology, BC Cancer Agency, Kelowna, BC, Canada, 3Molecular Medicine and Surgery, Karolinska University Hospital-Solna, Stockholm, Sweden

Background: Loco-regional recurrence (LRR) of breast cancer is a significant cause of morbidity and mortality. It is poorly described how prognosis after LRR has evolved over time at the population level.

Methods: 2272 patients diagnosed with LRR between 1980-2014 were identified within the Stockholm cancer registry and divided in 7 cohorts by the year of LRR diagnosis. Post-relapse event free survival (EFS) and overall survival (OS) were analyzed separately in local and loco-regional relapses and compared across the cohorts by Cox regression method. Primary tumor size, axillary node status, estrogen receptor (ER) status, type of surgery, adjuvant chemotherapy, LRR free survival, and age at LRR were the covariates for Cox model adjustment.

Results: In 1615 patients diagnosed with local relapse, 903 post-LRR events were registered (Table). A significant improvement in median EFS (p < 0.001) and OS (p < 0.001) was observed in patients diagnosed 2010-14 compared with previous time periods. Among 657 patients with loco-regional recurrences, 476 experienced a post-LRR event (Table). EFS and OS independently improved over time (p < 0.001 and p < 0.001, respectively). Smaller primary tumours, negative axillary lymph nodes, ER positive status, breast-conserving surgery, longer LRR-free interval and younger age at LRR occurrence were independently associated with longer survival after LRR. No association was observed between survival and type of surgery or LRR Free interval in LRR. An improvement in survival over time was also demonstrated when cohorts 1980-84 and 2010-14 were excluded from the model.

Legal entity responsible for the study: Samuel Martel
Background: The Phase III OlympiAD study showed a statistically significant and clinically meaningful PFS benefit with olaparib monotherapy, compared with standard of care chemotherapy (median 7.0 vs 4.2 months, respectively, hazard ratio 0.58; 95% CI 0.43, 0.80; P = 0.0009) in patients (Pts) with HER2-negative mBC and a gRcAM. A key predefined secondary objective was to assess the effect of olaparib on HRQoL.

Methods: The randomized, open-label, Phase III OlympiAD study (NCT02000622) enrolled Pts with HER2-negative mBC and a gRcAM, after ≥2 chemotherapy lines for mBC. Pts were randomized 1:1 to olaparib 300 mg twice daily (L) or placebo. A blinded independent adjudication of a physician’s choice (TPC) capite tabine, vinorelbine or etoposide. Pts were asked to complete an EORTC QLQ-C30 questionnaire (analysis focused on the Global HRQoL scale with range 0–100, and higher scores indicating a better QoL), at baseline and every 6 weeks until disease progression. Changes in Global HRQoL scores were analyzed descriptively, and mean change from baseline (cb) by a mixed model for repeated measures.

Results: 302 pts (ITT) were randomized to olaparib (n = 205) or TPC (n = 97). Overall QLQ-C30 compliance rate was 93% for olaparib vs 77% for TPC. HRQoL was better preserved with olaparib than TPC (mean cb in Global HRQol score across all-visit was 3.9 (n = 191) vs 3.6 (n = 73), respectively, difference 0.3; 95% CI 0.2, 0.5; P = 0.0005). The proportion of Pts (ITT) who were free of Global HRQol deterioration (cb decrease in ≥10 points) was 81.5% in the olaparib arm vs 61.2% in the TPC arm at 6 months, and 64% vs 53.5% at 12 months, respectively. The median time to Global HRQol deterioration was not reached in olaparib pts, and was 15.3 months for TPC pts. A best HRQol response of ‘improved’ (cb increase in >10 points over two ≥11 days apart) was observed in 34% olaparib pts vs 13% TPC.

Conclusion: Pts receiving olaparib experienced significantly less and later deterioration in Global HRQol than TPC. HRQol was modestly and consistently greater in patients receiving olaparib compared with TPC.

Clinical trial identification: Clinical trials no: NCT02000622

Release date: 18 November 2013

AstraZeneca name: OlympiAD

AstraZeneca number: DO819C00803

Legal entity responsible for the study: AstraZeneca

Funding: AstraZeneca


Results: As of 2/26/2016, median follow-up was 23.0 mo in pts receiving P+L. (n = 444). Median age of P+L pts was 62.0 (range, 30–89) years; ECOG status was 0, 1, and 2 in 57.9%, 40.1%, and 2.0%, respectively; and 213 (48.0%) received prior chemotherapy. 423 (95.3%) P+L pts experienced any grade (gr) NP, including 298 (70.4%) with gr 3/4 NP, manageable with dose modification. Among pts with gr 3/4 NP, 65 (15.4%), 41 (9.9%), and 192 (45.4%) experienced 2, or ≥3 episodes, respectively. 92 (20.7%) and 84 (18.9%) pts experienced ≥3 episodes of any grade anaemia and thrombocytopenia, respectively. Median (range) time to first episode of gr ≥3 NP, anaemia, and thrombocytopenia were 28.0 (12–854) median duration, 51.5), 182.9 d (14–760 [11.5]), and 283.4 d (21–617 [26.5]), respectively. Although NP was associated with increased risk of infection, the rate of gr 3/4 infections was 3.5% in P+L pts with NP. Of pts with gr 3/4 NP, 68.8% did not have any overlapping infections. Febrile NP was reported in 1.8% of P+L pts and did not result in therapy discontinuation. In univariate analysis, risk of developing gr 3/4 NP was associated with Asian ethnicity (P = 0.0002) and low baseline absolute neutrophil counts (P < 0.0001). NP resulting in dose reduction or interruption had no impact on PFS.

Conclusions: NP occurred early during therapy, and was manageable with dose modification. Febrile NP was reported in 1.8% of P+L pts and did not result in therapy discontinuation. Withholding dose, or dose reduction did not negatively impact PFS. Funding: Pfizer.
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529P Overall survival and quality of life in patients with metastatic breast cancer treated with nab-paclitaxel: Final results of the non-interventional study NABUCCO

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Background: Nab-paclitaxel (Nab-P) is approved for the treatment of metastatic breast cancer (MBC) after first line therapy and when anthracyclines are not indicated. Clinical trials proved high efficacy and reduced toxicity of Nab-P compared to standard taxanes. Real world data of Nab-P in MBC, however, are still limited. Methods: The prospective, multicenter, non-interventional NABUCCO study was designed to collect data on effectiveness including overall survival, safety, treatment patterns and quality of life (QoL) in patients (pts) with MBC in real world. QoL was assessed with the validated questionnaires Functional Assessment of Cancer Therapy-General (FACT-G) and the breast cancer and taxane specific modules (FACT-B and FACT-Taxane) at baseline (BL), 3, 6 months. Data were analyzed descriptively. Survival was analyzed with the Kaplan-Meier method. Results: 697 of 705 pts with MBC enrolled at 128 sites in Germany from 4/2012 to 4/2015 were evaluable (median age 62.3 years (yrs) (min-max 29.2-89.3); age ≥65 yrs n = 291 (41.8%), ECOG 0/1 n = 628 (90.1%), prior taxanes n = 419 (60.1%)); 194 pts (27.8%) received 220-260 mg/m² q3w, 491 pts (70.4%) received weekly nab-P at ≤ 150 mg/m² (physician’s discretion, 7% other). Median overall survival (mOS, months [95% CI]) was 15.6 [14.2-17.2]. No difference was observed with regard to treatment pattern (15.1 [12.3-17.3] q3w vs 16.3 [14.4-18.5] weekly) and age (15.7 [14.0-18.1] ≤65 yrs vs 15.1 [12.8-17.3] ≥ 65 yrs). mOS was significantly shorter in pts receiving prior taxanes (13.7 [11.7-15.5] vs 18.3 [16.4-22.2]) or prior chemotherapy in general (19.2 [16.9-22.2], 15.1 [12.5-17.3], 14.1 [10.3-17.2], 11.3 [9.1-12.7]) with 0, 1, 2, ≥ 3 prior palliative lines. Consistent with safety data, pts reported increased taxane-related symptoms after start of nab-P (BL vs 6 months; [range]: FACT-Taxane subscale score 52.3 [4.0-64.4] vs 44.0 [3.0-64.0]). Global and breast cancer related QoL were not affected (FACT-G 73.1 [27.0-105.0] vs 67.0 [14.0-104.0]; FACT-B subscale score 33.6 [0.0-35.0] vs 22.0 [2.0-35.0]). Conclusions: The NABUCCO study confirms survival data from clinical trials in real world without deteriorated global and breast cancer related QoL. Clinical trial identification: NCT02371174

Legal entity responsible for the study: IOMEDICO AG

Funding: Celgene

Disclosure: All authors have declared no conflicts of interest.

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Table: 294P Ribociclib PK parameters by PPI usea

<table>
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<th>n</th>
<th>PPI Use</th>
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<td></td>
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<td>Cmax (ng/mL)</td>
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<td>2,700 (53.0)</td>
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<td></td>
<td>Cmax (ng/mL)</td>
<td>6</td>
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<td>3,500 (65.8)</td>
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</table>

AUC0-24h, area under the concentration-time curve from time zero to 24 hours; Cmax, maximal concentration; PK, pharmacokinetics; PPI, proton pump inhibitor. "Defined by PPI use prior to and on the day of sampling on C1D15 for AUC0-24h, and Cmax and on the dosing date corresponding to the AUC0-24h, or Cmax. "Yes" was defined as PPI use for at least 5 consecutive days; "No" was defined as no PPIs use for at least 13 consecutive days.

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intensity on ribociclib bioavailability. The effect of a high-fat meal on ribociclib exposure was evaluated in a bioequivalence trial in healthy volunteers.

**Results:** Sensitivity analyses using validated PBPK models predicted no effect of varying stomach pH on ribociclib absorption. PK data (AUC[0–∞], Cmax) from several clinical studies showed similar ribociclib exposure regardless of PPI use (Table). The pop-PK analysis supported the PBPK models and clinical findings by showing that PPI use is a statistically insignificant and clinically unimportant covariate on ribociclib bioavailability. Food intake did not affect the rate or extent of ribociclib absorption.

**Conclusions:** In silico models and clinical PK data indicate that ribociclib can be administered without regard to PPI use or food intake. This lack of dosing restriction may facilitate greater patient compliance and clinical benefit.

**Legal entity responsible for the study:** Novartis Pharmaceuticals Corporation

**Funding:** Novartis Pharmaceuticals Corporation

**Disclosure:** T. Samant, M. Edlmiege, Y. Liu, S. Yang, M. Miller, C. Germa: Employee of Novartis Pharmaceuticals Corporation. S. Dhuria: Was an employee Novartis Pharmaceuticals Corporation at the time this study was conducted; currently a consultant for Novartis Pharmaceuticals Corporation. M. Laisney, A. Grandeury, M. Mueller-Zigmondy, K. I. Umehara, F. Huth: Employee of Novartis Pharma AG.

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295P Pneumocystis jiroveci pneumonia (PCP) in patients receiving weekly chemotherapy for metastatic breast cancer

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**Background:** Pneumocystis jiroveci pneumonia (PCP) is thought to be a rare phenomenon in the solid tumour population, particularly in patients with breast cancer. However, it may be increasing within this population as the type and intensity of chemotherapy used changes. There is currently a lack of consensus on PCP prophylaxis in patients who are immunocompromised due to chemotherapy.

**Methods:** The EPIC electronic health record system was searched for metastatic breast cancer (MBC) patients treated with a weekly chemotherapy (epirubicin/paclitaxel) regimen from October 2014 – February 2016 at Addenbrooke’s hospital (n = 49). A subset of patients diagnosed with PCP (n = 5) was identified. A retrospective analysis was performed on the charts of all patients.

**Results:** Patients received a mean of 21 weeks (SD = 15, min=1, max=62) of chemotherapy. An overall of 16% (n = 6) of patients had profound lymphopenia (absolute lymphocyte count <0.5*10^9/L) at some point during their treatment. 10% (n = 5) of the patients were diagnosed with confirmed (n = 3) and probable (n = 2) PCP.

**Conclusions:** In a high incidence of PCP was observed in MBC patients receiving weekly epirubicin/paclitaxel treatment. Additional investigation is needed to define the population of patients at the greatest risk of PCP infection, and to identify those who might benefit from antiretroviral prophylaxis.

**Legal entity responsible for the study:** Cambridge Cancer Centre

**Funding:** None

**Disclosure:** All authors have declared no conflicts of interest.

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296P Detection of early cardiac effects of docetaxel plus trastuzumab and pertuzumab through strain rate imaging in patients with HER2-positive metastatic breast cancer

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**Background:** Dual anti-HER2 therapy with trastuzumab and pertuzumab in combination with taxane-based chemotherapy improves overall survival in patients with metastatic HER2-positive breast cancer. There is a critical need to investigate the potential cardiotoxicity of dual anti-HER2 blockade, given the importance of HER2 signaling in cardiac homeostasis and stress response. Sequential left ventricular (LV) ejection fraction (EF) assessment has been mandated to detect myocardial dysfunction. Changes in cardiac function induced by this therapy, however, are subtle and difficult to quantitate by conventional imaging methods. Docetaxel myocardial imaging-based velocity, strain, and strain rate measurements have been shown to sensitively quantify abnormalities in cardiac function in other settings. The aim of this study was to determine if sensitive indices of left ventricular (LV) dysfunction, specifically strain rate imaging, would be useful for addressing the early detection of dual anti-HER2 mediated cardiotoxicity.

**Methods:** Patients with 0-1 lines of prior therapy were treated with 8 cycles of docetaxel (75mg/m^2) plus trastuzumab (8 mg/kg loading dose followed by 6 mg/kg) and pertuzumab (840 mg loading dose followed by 420 mg every 3 weeks. Conventional and Doppler myocardial imaging echocardiography were obtained at baseline and every 2 cycles of treatment. Segmental peak systolic longitudinal and radial velocity, strain, and strain rate (SR) were measured.

**Results:** Twenty-seven women (median age 52.2 years) were enrolled in the study. There was a significant change in Left ventricular dimension, ejection fraction, and systolic myocardial velocity. In contrast, a significant reduction in longitudinal and radial strain and strain rate was found after 8 cycles (longitudinal strain -12.8% +/- 2.2% vs baseline (P = .001); radial strain 29.3% +/- 7.1% vs 50.3% +/- 10.6%; P < .001 vs baseline). Changes in radial function appeared earlier and were more pronounced than in longitudinal direction.

**Conclusions:** In contrast with conventional echocardiography myocardial velocity measurements allowed detecting subtle changes in longitudinal and radial left ventricular function after 8 cycles of therapy. We suggest that strain rate imaging identifies pre-clinical myocardial dysfunction earlier than conventional measures in women undergoing treatment with dual anti-HER2 therapy for metastatic breast cancer and could be used for cardiac function monitoring.

**Legal entity responsible for the study:** Vasiliki Michalaki

**Funding:** None

**Disclosure:** All authors have declared no conflicts of interest.

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297P Evaluation of drug-drug interactions (DDI) between tucatinib and cabazitaxel (C) in patients with advanced HER2+ metastatic breast cancer from a phase 1b study

**A. Vo, D. Leviten, M. Insko, T. Sierra, A. Dazier, L. Walker, S. Peterson**

1DMPI, Cascadian Therapeutics, Inc., Seattle, WA, USA, 2ADME/PK, Cascadian Therapeutics, Inc., Seattle, WA, USA, 3Pharmacy, Cascadian Therapeutics, Seattle, WA, USA, 4Clinical Development, Cascadian Therapeutics, Inc., Seattle, WA, USA, 5Research and Development, Cascadian Therapeutics, Seattle, WA, USA

**Background:** Tucatinib is an orally bioavailable, potent HER2 selective tyrosine kinase inhibitor. Based on the combination activity with chemotherapy and trastuzumab (Tz) in preclinical HER2+ tumor models, tucatinib was evaluated in combination with Tz and C in a Phase 1b study in patients with HER2+ metastatic breast cancer (mBC).

**Methods:** A Phase 1b 3+3 dose escalation study (ONT-380-005) was conducted to evaluate the safety and tolerability of tucatinib in combination with C and Tz. Tucatinib (300 mg PO BID), C (1080 mg/m^2 PO BID 14 days of a 21-day cycle), and Tz (8 mg/kg IV loading, then 6 mg/kg IV once every 21 days), were administered to HER2+ mBC patients previously treated with Tz and T-DMI. Pharmacokinetic (PK) assessments were conducted on cycle 1 day 14 (+C) and on cycle 1 day 21 (+C). PK of C and its major cataloites/metabolites were also measured. In vitro assessments of the activation of C were determined in the presence of tucatinib. The enzymes evaluated were carboxyesterase (CES), cytidine deaminase (CDA), thymidine phosphorylase (TP), and dihydropyrimidinonephosphorylase (DPD).

**Results:** Tucatinib did not inhibit conversion of C to 5’-DFCR in vitro, at 10 μM tucatinib reduced ~30% of CES activity. Similarly, tucatinib did not have any significant effect on the activity of CDA, TP, or DPD. Results from PK inhibition studies suggested tucatinib does not have a measurable effect on the conversion of C to its active antimitabolite. The clinical PK of tucatinib was unchanged in the presence or absence of C. The PK of C and its cataloates/metabolites were also unaffected in the presence of tucatinib, and were consistent with reported literature.

**Conclusions:** The overall in vitro and clinical results indicate there is no evidence for DDI between tucatinib and C, including when the combination is given with Tz. The tucatinib-Tz-C triplet combination has been reported to be well tolerated and supports the evaluation of the efficacy of the combination regimen in an ongoing controlled, randomized, double-blinded registrational study (HER2CLIMB).

**Clinical trial identification:** ONT-380-005

**Legal entity responsible for the study:** Cascadian Therapeutics, Inc.

**Funding:** Cascadian Therapeutics, Inc.


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298P Outcomes of intracranial stereotactic radiotherapy (SRT) in metastatic breast cancer (BC)

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**Background:** Brain metastases (BM) are a significant cause of morbidity and mortality. Advancement of systemic therapies for patients with BC has improved control of extra-cranial metastases and survival. Intracranial control however continues to be challenging. SRT has been shown to provide excellent local control (LC) with minimal toxicity, although breast specific data is comparatively lacking.

**Methods:** This study aims to describe outcomes of first SRT including LC, distant brain control (DC), time to intracranial progression (TTP) and overall survival (OS) in a cohort of patients with BC who received SRT from 2001 to 2016 at the Royal Marsden Hospital. Kaplan Meier and log-rank methods were used for statistical analysis.

**Results:** 64 patients underwent SRT for 129 BM. Median age was 52.4 years. 58 (91%) were ECOG 0/1. 18 (28%) were hormone receptor positive (HR+) HER2 negative, 38 (59%) were HER2- enriched (HER2 2+), and 8 (12%) were evaluated in combination with trastuzumab. The median number of BM treated with SRT was 1 (range 1-12). Median dose and range was 20 Gy (12-35 Gy) in 1 fraction (1-10). 29 (45%) were treated using a linear
Eribulin is safe and efficient in metastatic breast cancer in elderly patients. Results from the REPROMELT multicentric retro-prospective cohort

Background: Treating metastatic breast cancer (MBC) in women of 70 years old or more is a frequent problem however few data are available describing the safety and efficacy of chemotherapy in elderly patients. Eribulin is validated for MBC from the 2nd line treatment onwards since two phase III studies. We present here a focus on safety and efficacy of eribulin in patients ≥70 years old compared to the results of younger patients in a real life cohort.

Methods: From Oct 2014 to Feb 2017, a multicentric retro-prospective study (REPROMELT) was conducted. Data concerning patient, tumor characteristics, previous treatments administered, tolerance, efficacy and outcome of eribulin were retrieved for patients treated in real life for MBC in 12 different French hospitals between Dec 2015 and Jan 2016. Data from 446 MBC patients were collected. This database was split in two cohorts comparing the results from the cohort of 363 patients of patients with albumine ≤30 g/L versus 13% in group A, without any statistical difference.

Results: Median age for each cohort was 56.3 and 75.4 years old. Both cohorts had similar tumour characteristics, number of metastatic sites and the median number of prior chemotherapies was 2. Albumine serum levels were lower in the group B with 21% of patients with albumine <35 g/L versus 13% in group A, without any statistical difference. Outcomes were similar in group A and B with respectively: median PFS of 3.67 months versus 3.7 months; HR 0.997 (CI 95% 0.762 -1.241), p = 0.010. Both cohorts received a median number of 4 cycles. The most frequent grade 3 adverse events were neutropenia (22.9% in group A and 15.7% in group B), fatigue (6.5% group A and 13.3% group B) and neuropathy (4.4% in A and 3.6%, respectively).

Conclusions: We present here the first study focusing retro-prospectively on the tolerance and efficacy of eribulin in elderly patients in real life. In this study, eribulin in patients ≥70 years old is as effective and safe as in younger patients.
Background: mCHT is the minimum biologically effective dose of a chemotherapeutic agent, given at regular dosing regimen with no prolonged drug free interval, that leads to anti-tumor activity. Old regimens included Cyclophosphamide-Methotrexate (CM), whereas in the last years new regimens, such as Vinorelbine (VRL) and Capecitabine (CAPE)-based have been developed. Aim of this observational retrospective ongoing study is to describe the use of mCHT in ABC pts across 5 years and the clinical characteristics of the pts together with efficacy of old (CM-like) vs new (VRL/CAPE-based) metronomic regimens in terms of response and disease control.

Methods: We retrospectively identified from clinical records those HER2-ve ABC pts who have received any kind of mCHT in the years 2011-2015, alone or in combination with a non-metronomic drug. Standard statistical approaches were used for describing the sample characteristics. Logistic and non proportional hazard analysis were used to identify factors associated with response, and time to treatment failure and survival, respectively. This preliminary analysis focuses on Response Rate (RR) and Disease Control Rate (DCR).

Results: From June 2011 to December 2015, 267 pts have been identified till now and 233 are fully evaluable. Median age at mCHT start was 67 years. 81% was HR+ and 33% had non-visceral metastatic disease. 22% of the pts received CM, 59% VRL-based and 23% mCAPE-based regimens. mCHT use increased over the time from 13.0% (2011) to 30.0% (2015). As 1st-line treatment, CM was administered in 27% of compared with more than 48% of patients receiving CAPE/VRL-based regimens. Overall Response Rate (ORR) was 28% and Disease Control Rate (DCR) was 79%. Median duration of mCHT was 6.2 months. New generation metronomic regimens produced higher ORR in comparison to old ones (32% vs 13.5%), with similar duration of treatment. New generation regimens were used in earlier lines of treatment, producing interesting results in terms of objective response and disease control.

Legal entity responsible for the study: Marina Elena Cazzaniga

Funding: ABO Consorzio per la riquisilazione agro-alimentare

Disclosure: All authors have declared no conflicts of interest.

Table: 302P Factors associated with prolonged time to treatment failure in fulvestrant 500 mg in patients with postmenopausal estrogen receptor-positive advanced/metastatic breast cancer (JBCRG-C06; Safari): A subgroup analysis

<table>
<thead>
<tr>
<th>ER+/HER2− (n=1072)</th>
<th>Hazard ratio (95% confidence interval)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (≥65/&lt;65 years)</td>
<td>0.85 (0.73–0.99)</td>
<td>0.035</td>
</tr>
<tr>
<td>Treatment line (≥4/3/2/1)</td>
<td>1.36 (1.22–1.52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time from diagnosis (≥3/&lt;3 years)</td>
<td>0.65 (0.54–0.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior chemotherapy (yes/no)</td>
<td>1.34 (1.13–1.58)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Conclusions: In ER+/HER2− patients who received F500 as ≥4 ≥3 ≥2 and ≥1-line treatment, advanced age, prior palliative chemotherapy and a longer time from AMBC diagnosis to F500 use were associated with longer TTF.

Clinical trial identification: UMIN000015168

Legal entity responsible for the study: Japan Breast Cancer Research Group (JBCRG)

Funding: Japan Breast Cancer Research Group (JBCRG) and AstraZeneca

Disclosure: H. Kawamura was a consultant to AstraZeneca Consulting fee/honorarium: Chugai, AstraZeneca, Eisai, Kyowa Kirin, Novartis, Taiho.

K. Aogi: Personal fees as honoraria: Chugai, Eisai, Sanofi, SRL, AstraZeneca, Taiho, Novartis, Daichi Sankyo, Mochida, Ono, Otsuka, and Eli Lilly Japan, and the institution received research funds from Chugai Pharmaceutical and AstraZeneca, and the institution received research funds from Chugai Pharmaceutical and Eisai. T. Nakayama: Lecture’s
In conclusion, we found that some patients showed no evidence of disease at 9.6 years. The median duration of trastuzumab therapy for all 27 patients was 5.1 years (0.9-9.3 years).

Disease progression occurred in 4 of the 27 patients after the interruption of trastuzumab treatment. The causes were disease progression to unknown reasons for 3 patients, and at the request of 1 patient. Disease progression was treated with chemotherapy in 2 patients and with endocrine therapy in 2 patients. The causes of death were disease progression in 9 patients and other causes in 1 patient. Disease progression was treated with chemotherapy in 8 patients and with endocrine therapy in 2 patients.

Conclusion: The results of this study suggest that the extension of trastuzumab therapy beyond 5 years could be considered for some patients with HER2-positive breast cancer.

Disclosure: All authors have declared no conflicts of interest.

A. Makhtar
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Background: Over the last six decades, metformin has become one of the most widely prescribed oral medications for type II diabetes. It has recently received considerable attention because of its potential role in reducing the risk of cancer development and its antinflammatory properties. However, the mechanism behind the growth-inhibitory effect of metformin on breast cancer cells remains unclear, with little consensus on which tumour subtypes benefit from treatment. Furthermore, it should be noted that much of the in vitro work published to date has used drug concentrations greatly exceeding the recommended clinical dose, and therefore may not translate directly into clinical practice.

Methods: Non-tumorigenic (MCF10A), pre-malignant (MCF10AT), pre-invasive (DCIS), the three-invasive breast cancer (MCF7, T47D and MDA-MB-231) and the fully bone-homologous variant of MDA-MB-231 (BM) were treated with metformin and effects on cellular proliferation were evaluated by trypan-blue exclusion and clonogenic assays. The expression levels of metformin transporters mRNA and proteins (OCT1-3, MATE1-2 and PMAT) were evaluated by qRT-PCR, western blot.

Results: The growth-curtailing effect of metformin was achieved at 0.3 mM for MDA-MB-231 (P = 0.0198) in cell counting assays. Colony-forming capacity was inhibited in all cell lines tested at 0.3 mM (P < 0.0001). The invasive cancer cells demonstrated strong expression of OCT2, PMAT and MATE1 but minimal positivity for OCT1 and no expression of MATE2. OCT3 is only expressed by the triple negative MDA-MB-231. The mRNA and tissue expression of metformin transporters followed the same pattern. Clinically relevant doses of metformin inhibited the proliferation and colony formation of different breast cancer subtypes regardless of their receptor status and aggressiveness, including the hard to treat triple negative subtype MDA-MB-231 cells. Expression of various influx and efflux metformin-transporters is essential for cellular metabolism and proliferation.

Conclusion: Clinically relevant doses of metformin inhibited the proliferation and colony formation of different breast cancer subtypes regardless of their receptor status and aggressiveness, including the hard to treat triple negative subtype MDA-MB-231 cells. Expression of various influx and efflux metformin-transporters is essential for cellular metabolism and proliferation.

Legal entity responsible for the study: Libyan higher ministry of education

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Abstracts
(n = 23 and 16). Neuropathy G3/4 was mostly reported in 3-w-P and w-P arm than in V arm (75% vs. 69% vs. 17%). G3/4 alopecia was reported in both P arms (94%) when in V arm G3 alopecia was only in 6% of pts.

Conclusions: Weekly Paclitaxel appeared as effective as every-3-weeks regimen and weekly Vinorelbine, however neurotoxicity is a treatment-limiting toxicity for both Paclitaxel regimen. Vinorelbine had fewer significant grade 3-4 toxicities than both Paclitaxel arms and had better RR. Larger randomised studies are needed to determine the efficacy and overall survival of Paclitaxel versus Vinorelbine. Legal entity responsible for the study: Lika Katselashvili

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Table: 307P

<table>
<thead>
<tr>
<th>Category Variable</th>
<th>CBR, n (%)</th>
<th>ORR, n (%)</th>
<th>PFS, median (range)</th>
<th>OS, median (range)</th>
<th>Dose adjustments, n (%)</th>
<th>TRAE withdrawals, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25 (53.2)</td>
<td>11 (23.4)*</td>
<td>3.6 (2.4 – 4.9)</td>
<td>12.1 (9.6 – 19.1)</td>
<td>9 (19)</td>
<td>3 (6)*</td>
</tr>
<tr>
<td>TRAE: treatment related adverse events.</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

*Including 1 complete response. **Most TRAE were of hematologic origin.

Conclusions: HALATRUST is, to the best of our knowledge, the largest reported case series on the use of eribulin plus trastuzumab for the treatment of late-line HER2 (+) MBC. Results found provide clear evidence on the efficacy and safety of the combination, and highlight the need for its inclusion within the earlier treatment options used in this patient population.

Clinical trial identification: EIS-ERI-2016-01

Legal entity responsible for the study: Eisai Pharmaceuticals Spain

Funding: Eisai Pharmaceuticals Spain

Disclosure: L. Orcajo Rincón, J. Rodríguez-Villanueva: Employee of Eisai Pharmaceuticals. All other authors have declared no conflicts of interest.

308P

Lower response to T-DIM in metastatic breast cancer patients with HER2 IHC score of 2 and FISH positive compared with IHC score of 3

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Background: Ado-trastuzumab emtansine (T-DIM) is the standard second line chemotherapy for HER2 overexpressed metastatic breast cancer (MBC). Tumor HER2 status is measured by either immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH). A previous study showed no difference in objective response rate (ORR) with trastuzumab monotherapy between IHC 3+ and IHC 2+/FISH positive groups. It is not known whether response to T-DIM-1 differs between IHC 3+ and IHC 2+/FISH positive patients. The aim of this study is to compare the efficacy of T-DIM in IHC 3+ group to that of IHC 2+/FISH positive group.

Methods: We retrospectively identified and reviewed the medical records of all patients with HER2 positive MBC who received T-DIM in our hospital from October 2013 to December 2016. In the efficacy analysis, we excluded five patients who had HER2 negative tumors at metastatic sites.

Results: A total of 44 patients were identified and 36 patients were available for efficacy analysis of ORR. Median age was 58 years old (range 28-80). 95.5% received prior trastuzumab. 45.5% received at least one chemotherapy for MBC. 29.5% received more than four lines of chemotherapy. 79.9% had IHC 3+ and 20.5% had IHC 2+/FISH positive. ORR was 16/30 (53.3%) in IHC 3+ group and was 0/6 (0%) in IHC 2+/FISH positive group (P = 0.024). Median progression free survival (PFS) was 7.0 months (95% CI, 5.8 to 8.42) in IHC 3+ group and was 2.0 months (95% CI, 0.00-4.57) in IHC 2+/FISH positive group.

Conclusions: ORR and PFS were significantly worse in HER2 IHC 2+/FISH positive patients compared with IHC 3+ patients. This is the first report to demonstrate the difference of T-DIM efficacy by HER2 test results.
309P

**Nab-paclitaxel (Nab-P) in HER2-positive breast cancer (ABC) patients (pts): From randomized trials to real-life setting: Results from GIM13 - AMBRA study**

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**Background:** Two randomized studies demonstrated that Nab-P produces a significantly higher overall response rate (ORR), longer progression-free survival (PFS), and greater overall survival (OS) in ABC pts treated with second-line or greater therapy compared with patients who receive conventional Paclitaxel. However, few data are available in the real-life setting, especially for the weekly schedule (wN-P). Methods: AMBRA is a longitudinal cohort study, aiming to describe the choice of first and subsequent lines of treatment in HER2+ ABC pts receiving at least one CHT therapy. Results: So far, 791/1500 pts have been registered into the study and 107 (13.5%) received Nab-P in any line of treatment. Median age was 54 years, 88 (82.2%) had Luminal tumours. Twenty-two pts (20.6%) received Nab-P as 1st line, 48 (44.8%) as 2nd line, the remaining as 3rd line or greater. Most pts (47.7%) received the every 3 weeks (Q21) schedule, whereas 30 pts (28%) were treated with the weekly (wN-P) schedule (days 1,8,15 Q28) at different doses: £100 mg/m²: 11 (10.3%), 125 mg/m²: 15 (14%); 150 mg/m² 4 (3.7%). The remaining received different schedules or doses. Median number of cycles was received 5 (1-7) and median duration of treatment was 3.5 months in the whole population. No difference has been observed in term of number of cycles or duration of treatment according to the schedule. Conclusions: Our results are similar to those obtained in randomized clinical trials and in a recent large real-life study, confirming that Nab-P is currently one of the most promising choice of treatment for ABC pts. Legal entity responsible for the study: Mediterranea Oncology, University of Cagliari, Cagliari, Italy, 2Medical Oncology, Università degli studi di Cagliari, Cagliari, Italy, 3Hospital Management, Sede Centrale di Ortopedia - Ospedale di Cagliari, Cagliari, Italy, 4Medical Oncology, Ospedale Civile di Cuneo, Cuneo, Italy, 5Medical Oncology, Università degli Studi di Pisa, Pisa, Italy, 6Medical Oncology, Azienda Ospedaliera Arcispedale S. Annunziata - Università degli Studi di Siena, Siena, Italy, 7Medical Oncology, Università degli Studi di Bologna, Bologna, Italy, 8Medical Oncology, Azienda Ospedaliera di Parma, Parma, Italy, 9Medical Oncology, Università degli Studi di Firenze, Firenze, Italy, 10Medical Oncology, Università degli Studi di Pisa, Pisa, Italy, 11Medical Oncology, Azienda Ospedaliera Arcispedale S. Anna, Bologna, Italy, 12Medical Oncology, Università degli Studi di Firenze, Firenze, Italy, 13Medical Oncology, Università degli Studi di Padova, Padova, Italy, 14Medical Oncology, Università degli Studi di Milano, Milan, Italy, 15Medical Oncology, Università degli Studi di Bologna, Bologna, Italy, 16Medical Oncology, Università degli Studi di Siena, Siena, Italy, 17Medical Oncology, Università degli Studi di Bologna, Bologna, Italy, 18Medical Oncology, Università degli Studi di Firenze, Firenze, Italy, 19Medical Oncology, Università degli Studi di Bologna, Bologna, Italy.

Legal entity responsible for the study: St. Luke’s International Hospital

Funding: None

Disclosure: All authors have declared no conflicts of interest.

310P

**Everolimus-exemestane (EE) vs palbociclib-letrozole (PL) or palbociclib-fulvestrant (PF) in the treatment of metastatic HR+ , HER2- breast cancer: An indirect comparison with network meta-analysis**

*C. Cherubini1, L. Gianni1, L. Stocchi1, V. Arcangeli1, O. Carminati1, M. Pap2, G. Pasini1, M. Fantini1, S.V.L. Nicoletti1, D. Tassani1.

**Background:** To compare the efficacy of EE to PF or PL in the treatment of metastatic HR+, HER2- breast cancer. An indirect comparison with network meta-analysis (NMA) was performed. Methods: An indirect comparison with network meta-analysis comparing EE with PL or PF in the treatment of metastatic HR+, HER2- breast cancer pre-treated or untreated with aromatase inhibitors (AI) for advanced disease was performed. Results: The progression-Free Survival (PFS) was the primary end point of all our indirect comparisons. The indirect comparison was performed both for patients pre-treated with AI and for patients never treated with AI for advanced disease. Efficacy data were expressed as Hazard Ratio (HR) and 95% Confidence Interval (95%CI), assuming an α-error of 5% as index of statistical significance. Results: All the data of the BOLERO-2 trial, the Bachelot et al network meta-analysis (Breast Cancer Treat Rep 2014), the PALOMA-2 and the Paloma-3 trial were analyzed and indirectly compared in a network meta-analysis. 2 orders of comparison were performed: EE vs PL for patients never treated with AI for advanced disease and EE vs PF for patients pre-treated with AI for advanced disease. The pooled HR and 95%CI were respectively 0.987 (0.855-1.100, p = 0.53) and 1.07 (0.71-1.6, p = 0.8) for EE vs PL (never treated with AI) and EE vs PF (pre-treated with AI). No major reasons of clinical and methodological heterogeneity were detected in an independent qualitative analysis, while a moderate quantitative heterogeneity was detected using the I² test. Conclusions: ToHRR2 breast cancer treated or untreated with AI, and no direct comparisons between EE and PL or PF exist in literature. Although our data have not the power to detect any definitive difference in PFS between EE and PL or PF (probably with the exception of EE vs PL, where a trend in favor of EE could be detected), EE, PL or PF seem to be comparable in terms of PFS; it follows that the better safety or the economic profile could help physicians in daily clinical practice. Legal entity responsible for the study: Studio Tassinari

Funding: None

Disclosure: All authors have declared no conflicts of interest.

311TP

**FRIEND: A randomized pilot study to compare the efficacy and tolerability of fulvestrant 500mg with exemestane as first line endocrine therapy for post-M HR positive HER2 negative ABC patients relapse after adjuvant non-steroidal aromatase inhibitors (NSAI)**

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**Background:** Breast cancer is one of the most common malignancies in women. It has long been acknowledged that oestrogen acts as an endocrine growth factor for hormone-dependent breast cancer. Fulvestrant is a selective estrogen receptor degrader – an ER antagonist with a novel mode of action. Confirms & China Confirm study demonstrated that the efficacy of Fulvestrant 500mg is superior to 250mg. First &Falcondon study results confirmed the superior efficacy of fulvestrant over anastrozole in postmenopausal women who have not received prior hormonal therapy. But in the clinical practice, AI are widely used as adjuvant EE for postmenopausal ER+ breast cancer patients. To date there are no randomized trials to compare Fulvestrant 500mg with AI in patients who have relapsed or during after adjuvant non-steroidal AI. Trial design: The FRIEND trial is a parallel-group, multi-centre study designed to compare the efficacy and tolerability of fulvestrant 500 mg with exemestane 25 mg as first line endocrine therapy in post-M women with ER positive HER2 negative ABC who have relapsed on or after less than 2 year of adjuvant NSAI therapy. Approximately 148 postmenopausal women with ER positive HER2 negative advanced breast cancer who have relapsed whilst on adjuvant NSAI (treatment duration ≥ 2 years) or after completed adjuvant NSAI treatment will enter this study. Eligible patients will be randomized 1:1 to the following treatment groups: Fulvestrant 500 mg i.m. every 28 (± 3) days plus an additional 500 mg on day 15 (± 3) of first month only; Exemestane 25 mg, orally, once daily. Treatment will continue until disease progression or treatment discontinuation. The primary endpoint is progression-free survival. Secondary endpoints include objective response rate, disease control rate, time to treatment failure, duration of response and overall survival. Efficacy will be determined based on tumor assessments performed by each investigator according to RECIST version 1.1. Safety will be monitored based on the frequency and severity of adverse events (ADs). This study is currently recruiting patients.

Clinical trial identification: NCT02646735

Legal entity responsible for the study: NA

Funding: AstraZeneca China

Disclosure: All authors have declared no conflicts of interest.
(VRL) is a well-established cytotoxic drug. There is a high medical need for new options that prolong the time between endocrine failure and intensive CTX, which is commonly associated with impaired quality of life and serious side effects. Metronomic CTX was shown to induce disease control in aMBC with a favorable safety profile. This innovative approach involving continuous daily dosing of oral VRL, which could provide anti-angiogenic and immune-modulatory properties, has not been investigated so far in this indication.

Trial design: VinoMetro is an open-label, single-arm, phase II study (Simon two-stage mininum) of metronomic daily oral VRL (30 mg/day) as first-line CTX. The study involves strict safety monitoring with an initial safety run-in. It is accompanied by a steering committee and supervised by an independent monitoring board. The main objectives are to estimate efficacy in terms of clinical benefit rate after 24 weeks of treatment (primary endpoint) and the progression-free survival, amongst others, as well as the assessment of safety and quality of life. Patients with HR+/HER2- aMBC having failed or being no candidate for endocrine therapy (targeted combinations allowed) and being naive to palliative CTX are eligible, if they exhibit ECOG 0-1. The main exclusion criteria are prior vinca-alkaloids, aggressive disease requiring combination CTX and CNS involvement. Until 2017/04–30, 5 patients were enrolled. It is planned to include 45 (39 evaluable) patients at 8 German sites until 09/2018. Scheduled completion date is 09/2019. Two interim analyses are planned (first analysis: safety evaluation based on 15 patients; second analysis: safety evaluation based on 30 patients).

Clinical trial identification: EuDrAC 2016-000284-17

Legal entity responsible for the study: University Medical Centre of Johannes Gutenberg-University Mainz, Germany

Funding: Pierre Fabre Pharma GmbH, Freiburg, Germany

Disclosure: T. Elger, M. Seehase, L. Schollenberger, C. Ruckes, M. Schmidt: Gutenberg-University Mainz, Germany

Legal entity responsible for the study: University Medical Centre of Johannes Gutenberg-University Mainz, Germany

Funding: Pierre Fabre Pharma GmbH, Freiburg, Germany

Disclosure: T. Elger, M. Seehase, L. Schollenberger, C. Ruckes, M. Schmidt: Gutenberg-University Mainz, Germany

313TP Open-label phase II study of everolimus plus endocrine therapy in post-menopausal women with ER+ HER2- metastatic breast cancer (Chloe trial)

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Background: BOLEO-2 trial demonstrated that the mTOR inhibitor everolimus was effective in overcoming resistance to endocrine therapy, and BOLEO-4 trial is evaluating the efficacy and safety of combined use of everolimus with letrozole as initial therapy for ER positive HER2 negative metastatic breast cancer (MBC). However, there is no study to evaluate the efficacy of everolimus which can prolong the administration period of aromatase inhibitor (AI) through postponing the acquisition of drug-resistance for MBC with sensitivity to aromatase inhibitor.

Trial design: This study is conducted to examine whether additional administration of everolimus significantly prolongs progression-free survival period in post-menopause patients with ER-positive HER2-negative MBC which have sensitivity to AI. The inclusion criteria are MBC pts with histologically confirmed ER positive and HER2 negative breast cancer with one or more measurable distant metastases diagnosed by radiological examination. All patients are receiving AI as the first line hormone therapy for 5-7 months. The pts who are sensitive to AI are randomized to everolimus plus AI arm or the AI alone arm. After randomization, the same AI are continued until progression of disease and non-adherent regimens are started after that. The primary endpoint is the progression free survival, and the secondary endpoints are overall survival, response rate, disease control rate, adverse events, time to treatment failure and the proportion of patients who continued administration of AI agents for 1 year after the randomized allocation. Sample size for randomized pts is determined to attain at least 80% of power to detect a 3 months’ difference (10 vs. 15 months, HR0.65) with one-sided alpha of 0.1. Enrollment of 130 pts for randomization is planned over a 2-year accrual period from April 2017.

Clinical trial identification: This trial was registered at UMIN-CTR[umin.ac.jp/ctr/] as UMIN00002516.

Legal entity responsible for the study: Comprehensive Support Project for Oncological Research of Breast Cancer

Funding: Novartis

Disclosures: T. Toyama: Research funds from Novartis, Kyowa Hakko Kirin, Dichi Sanky, Ezaai, Chugai, Hippon Kayaku and Takeda Co. All other authors have declared no conflicts of interest.

314TP Selecting patients with oligo-metastatic breast cancer harboring homologous recombination deficiency (HRD) for intensified chemotherapy: The OLIGO-study

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Background: About 9% of patients with metastatic breast cancer (MBC) survive more than 10 years. Long-term survival is mostly seen in patients with limited, maximum of 3-5, distant metastases, often referred to as ‘oligo’-MBC. Oligo-metastatic cancer can be treated with curative intent using a multidisciplinary approach that targets the detected metastases, circulating micro-metastases, and any locoregional disease if present. Optimal patient selection is of vital importance.

Intensified chemotherapy in the treatment of breast cancer is controversial, as older studies have not shown a survival benefit in unselected patients. Recent retrospective analyses, however, have suggested that patients with HRD derive significant benefit from intensified chemotherapy compared to conventional chemotherapy.

Trial design: This study will evaluate the difference in event-free survival (EFS) between intensified chemotherapy and conventional chemotherapy as part of a multi-arm treatment approach in patients with oligo-MBC harboring HRD. Patients are eligible if they have pathological proven oligo-MBC, defined as ≤ 3 distant metastases, either as de novo or recurrence for which no chemotherapy is given. All lesions must be amenable to surgery or radiotherapy with curative intent. No progression on induction chemotherapy is allowed. Lastly, the tumor has to be HRD by array comparative genomic hybridization. Patients start with 3 cycles of induction chemotherapy, which includes anthracyclines and taxanes in treatment-naive patients and is adapted according to previously received (neo)adjuvant treatment in patients. Patients are 1:1 randomized to another 3 cycles of conventional chemotherapy or 2 cycles of intensified chemotherapy (carboplatin, thiopeta and cyclophosphamide) with stem cell support. Following systematic treatment, all patients receive maximal surgery and/or radiotherapy of locoregional and distant disease. The primary endpoint is EFS at 3 years. Toxicity, time to progression, and overall survival are secondary clinical endpoints. In total 86 patients are required. At the time of abstract submission, 33 patients were randomized.

Clinical trial identification: NCT01646034

Legal entity responsible for the study: The Netherlands Cancer Institute

Funding: Dutch Cancer Society (KWF)

Disclosures: S.C. Lin: Grants and non-financial support from AstraZeneca, Roche, Genentech, Cergentix. Advisory support from Novartis, PhilipsHealth and IBM outside the submitted work. A BRCA-like signature-patent (WO/2015/080585 and PCT/ NL2014/058013) is pending. G.S. Sonke: Institutional research support funding from Roche, AstraZeneca, Merck and Novartis. All other authors have declared no conflicts of interest.

315TP AGATA molecular screening program: Implementing precision medicine in patients with advanced breast cancer in Spain

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Background: About 5% of patients with metastatic breast cancer (MBC) survive more than 10 years. Long-term survival is mostly seen in patients with limited, maximum of 3-5, distant metastases, often referred to as ‘oligo’-MBC. Oligo-metastatic cancer can be treated with curative intent using a multidisciplinary approach that targets the detected metastases, circulating micro-metastases, and any locoregional disease if present. Optimal patient selection is of vital importance.

Intensified chemotherapy in the treatment of breast cancer is controversial, as older studies have not shown a survival benefit in unselected patients. Recent retrospective analyses, however, have suggested that patients with HRD derive significant benefit from intensified chemotherapy compared to conventional chemotherapy.

Trial design: This study will evaluate the difference in event-free survival (EFS) between intensified chemotherapy and conventional chemotherapy as part of a multi-arm treatment approach in patients with oligo-MBC harboring HRD. Patients are eligible if they have pathological proven oligo-MBC, defined as ≤ 3 distant metastases, either as de novo or recurrence for which no chemotherapy is given. All lesions must be amenable to surgery or radiotherapy with curative intent. No progression on induction chemotherapy is allowed. Lastly, the tumor has to be HRD by array comparative genomic hybridization. Patients start with 3 cycles of induction chemotherapy, which includes anthracyclines and taxanes in treatment-naive patients and is adapted according to previously received (neo)adjuvant treatment in patients. Patients are 1:1 randomized to another 3 cycles of conventional chemotherapy or 2 cycles of intensified chemotherapy (carboplatin, thiopeta and cyclophosphamide) with stem cell support. Following systematic treatment, all patients receive maximal surgery and/or radiotherapy of locoregional and distant disease. The primary endpoint is EFS at 3 years. Toxicity, time to progression, and overall survival are secondary clinical endpoints. In total 86 patients are required. At the time of abstract submission, 33 patients were randomized.

Clinical trial identification: NCT01646034

Legal entity responsible for the study: The Netherlands Cancer Institute

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Disclosures: S.C. Lin: Grants and non-financial support from AstraZeneca, Roche, Genentech, Cergentix. Advisory support from Novartis, PhilipsHealth and IBM outside the submitted work. A BRCA-like signature-patent (WO/2015/080585 and PCT/ NL2014/058013) is pending. G.S. Sonke: Institutional research support funding from Roche, AstraZeneca, Merck and Novartis. All other authors have declared no conflicts of interest.

AGATA molecular screening program: Implementing precision medicine in patients with advanced breast cancer in Spain
prospectively sequencing a large panel of genes and utilizing this information to guide treatment choices may improve the outcome of a subset of patients. Some institutions are implementing such strategy as part of the routine treatment decision-making process. However, SOLTI, as a collaborative Spanish network, runs AGATA, the first multi-institutional molecular screening program ever implemented in this country. Patient recruitment started in October 2014 and is expected to conclude in June 2017. Trial design: Up to 260 patients with metastatic breast cancer will be recruited in 10 participating sites in Spain. Mutation testing is performed prospectively in the genomic laboratories of Vall d’Hebron Institute of Oncology in Barcelona, 12 de Octubre University Hospital in Madrid, and the University Clinical Hospital of Valencia. Upon molecular characterization and collection of clinical data, each case is reviewed by a multidisciplinary advisory board, which recommends potential experimental treatments, mainly in the context of clinical trials. During this pilot stage, our primary objective is to determine the success rate in including patients in trials based on their molecular profile. Additional aims are to identify technical and logistical barriers to the implementation of a nationwide program, describe the genomic profiles of the tumors, and assess patient outcomes. Retrospective gene expression (PAM50) + 110 genes and 20 mRNAs and homologous recombination repair gene mutations (HRRm) in HER2-ve mBC pts is not well defined. Treatment patterns and survival outcomes for pts with HRRm will also be examined. Clinical trial identification: NCT02445482

Legal entity responsible for the study: SOLTI Breast Cancer Research Group

Funding: Novartis, Mutua Madriléria, Instituto de Saúde Carlos III

Disclosure: All authors have declared no conflicts of interest.

316TPB

BREAKOUT: A cross-sectional, prospective, observational study of germline BRCA mutation (gBRCAm) prevalence and real-world outcomes among patients (pts) with HER2-negative (HER2-ve) metastatic breast cancer (mBC)

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Background: Chemotherapy (including paclitaxel [pacl]) remains the main 1L treatment for metastatic TNBC but brings limited clinical benefit, highlighting the need for new treatments. Atezolizumab (atezo) blocks the interaction of PD-L1 with receptors PD-1 and B7.1, thus restoring anti-tumor immunity. TNBC is a rational target for atezo due to high PD-L1 expression, elevated T-cell tumor infiltration and high mutational burden. Atezo alone and in combination with nab-pacl was well tolerated, with no exacerbation of chemo-associated adverse events, and demonstrated promising clinical activity in mTNBC. Atezo + nab-pac is being further investigated as 1L TNBC treatment in MP3131. Breakout, a global, multi-center, randomized, double-blind, placebo (pbo)-controlled study, is comparing the efficacy and safety of 1L atezo + paco vs pbo + pac in patients (pts) with untreated, inoperable, locally advanced or metastatic TNBC.

Trial design: Eligible pts are those with inoperable, locally advanced or metastatic TNBC, histologically confirmed; de novo or recurrent disease after early BC chemo treatment completed ≥ 12 mo prior; taxane monotherapy eligible; no prior chemo or targeted systemic therapy for inoperable locally advanced or metastatic disease; ECOG PS 0-1 and measurable disease by RECIST v1.1. Exclusion criteria include known symptomatic CNS disease, prior immunotherapy and history of autoimmune disease. Approximately 495 pts will be randomized 2:1 to receive atezo (840 mg) or pbo (q2w; days 1 and 15 of 28-day cycle) plus paco (90 mg/m2; days 1, 8, 15 of 28-day cycle) until disease progression. Stratification factors are PD-L1 expression on tumor-infiltrating immune cells (IC; IC0 [1%] vs IC1/2/3 [≥ 1%] with VENTANA SP142 IHC assay), prior taxane therapy, presence of liver metastases and geographical region. The primary endpoint is PFS measured by RECIST v1.1. Key secondary endpoints include OS, 12- and 18-month OS rates, 12-month PFS rate, ORR, DOR, and safety. Tumor biopsies will be investigated at baseline, on treatment and at progression to assess biomarkers of response and immune escape.

Clinical trial identification: NCT03125902

Legal entity responsible for the study: F. Hoffmann-La Roche Ltd.

Funding: F. Hoffmann-La Roche Ltd.

Disclosure: D. Miles: Honors for Advisory Boards from Roche-Genentech. F. Andre: Research grants: AstraZeneca, Novartis, Pfizer, Roche. Granted research: Eisai, Roche, D. Cameron: Employer paid for consultancy work done with Roche. Hospital has also been reimbursed for costs incurred in doing clinical research by Roche. C.H. Barrios: Research: Pfizer, Novartis, Amgen, AstraZeneca, Boehringer Ingelheim, Roche, Lilly, Sanofi, GSK, Taibo, Mylan, Merck, Astellas, Bristol-Myers Squibb. Consulting: Boehringer-Ingelheim, GSK, Novartis, Genentech, Eisai. A. Schneeweiss: Member of Roche advisory boards. Member of IMP3130 steering committee. Honors and financial support from Roche for presentations at academic meetings. V. Easton, J. Dalvo: Roche employee and stock. J. O'Shaughnessy: Consultant to Genentech and Roche. All other authors have declared no conflicts of interest.
Background: CDK4/6 inhibitor ribociclib was recently approved in the United States in combination with letrozole for the treatment of HR+ HER2– ABC in postmenopausal women with no prior endocrine therapy (ET) for ABC. RCTs of combining trastuzumab plus palbociclib, with or without letrozole, assessed by PFS6. Assuming an increase of at least 20% in PFS6 by the addition of palbociclib to trastuzumab plus letrozole, 200 patients are needed to show non-inferiority. The trial is designed and powered for superiority.

Trial design: This open-label, multicentre, double-blind phase III trial randomizes patients in a 2:1 ratio to trastuzumab plus letrozole or trastuzumab plus letrozole plus palbociclib. The primary endpoint is progression-free survival (PFS) as the time from randomisation to documented disease progression or death from any cause. Secondary endpoints are safety, tolerability, and the proportion of patients achieving clinically meaningful benefit in pre-defined subgroups. The trial is conducted in 32 countries in North America, Europe, and Australia.

319TIP CompLEEment-1: Phase 3b study of ribociclib + letrozole for the treatment of hormone receptor-positive (HR+)/human epidermal growth factor receptor 2 negative (HER2-) advanced breast cancer (ABC) in patients with no prior endocrine therapy (ET) for ABC

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A phase II trial of mirvetuximab soravtansine in patients with localized triple-negative breast cancer (TNBC) with tumors predicted insensitive to standard neoadjuvant chemotherapy (NACT) including a lead-in cohort to establish activity in patients with metastatic TNBC

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Background: While TNBC patients with pCR/RCB-0 or RCB-1 have excellent survival, those with extensive residual disease (RCB-II or RCB-III) after NACT have poor prognosis. At MD Anderson, through the Moonshot Initiative, we have created a biomarker-driven drug development strategy, ARTEMIS (A Randomized, TNBC Enrolling trial to confirm Molecular profiling Improves Survival) to identify novel targeted therapies for tumors that are predicted to be insensitive to standard NACT. Molecular profiling along with imaging is used to identify patients with chemoresistant disease and inform second phase of therapy incorporating targeted agents to improve responses. Folate receptor α (FRα) is a GPI anchored surface protein encoded by FOLR1 gene that is overexpressed in multiple cancers including TNBC. Mirvetuximab soravtansine is an antibody-drug conjugate that consists of a monovalent antibody against FRα conjugated to maytansinoid, a microtubule inhibitor. Nearly 40% of TNBC express high levels of FRα, suggesting that FRα directed therapy is a viable therapeutic strategy.

Trial design: The study will include a lead in cohort (Cohort A) to establish efficacy in metastatic TNBC patients and a neoadjuvant cohort (Cohort B) to determine activity in chemosensitive, localized TNBC patients. If >2 patients in Cohort A have response, the neoadjuvant cohort will be activated. Patients deemed to have chemoresistant, FRα+ TNBC identified through the ARTEMIS are eligible for Cohort B. The primary objectives are to determine the response rate of single agent mirvetuximab in metastatic FRα+ TNBC (>2 lines of therapy) and to determine if mirvetuximab would improve the rates of neoadjuvant pathologic response (pCR or RCB-1) from 5% to 20% in patients with high risk, chemoresistant, ERα+ TNBC. A two-stage Gehan-type design with 14 patients in the first stage will be employed for the neoadjuvant cohort (n = 37). Mirvetuximab will be given IV every 21 days (6 mg/kg). Correlates include assessment of FOLR1/FRα and characterization of biomarkers of immune modulation.

Clinical trial identification: NCT03106077
Legal entity responsible for the study: M.D. Anderson Cancer Center Funding: NCIEN

Disclosure: All investigators have declared no conflicts of interest.

320TIP SOLTI-1303 PATRICIA: A phase II study of palbociclib and trastuzumab (with or without letrozole in ER+) in previously trastuzumab-pre-treated, postmenopausal patients with HER2-positive metastatic breast cancer

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Background: Despite the high efficacy of anti-HER2 agents, HER2+ metastatic breast cancer remains incurable and in need of additional therapeutic options. Persistent activation of the cyclin D1/CDK4/6 axis has been identified as a mediator of resistance to anti-HER2 therapy but clinical data of the benefit of CDK4/6 inhibitors in combination with trastuzumab is lacking. PATRICIA is a Simon 2-Stage study to evaluate the efficacy of combining trastuzumab plus palbociclib, with or without letrozole, assessed by progression-free survival (PFS) in pretreated HER2-positive patients.

Trial design: Postmenopausal HER2-positive patients treated with 2-4 prior systemic anticancer treatment lines that must involve trastuzumab or another anti-HER2 treatment in the metastatic setting are included in three cohorts: A: HR-negative, receiving trastuzumab and palbociclib, B1: HR-positive, receiving trastuzumab and palbociclib, B2: HR-positive, receiving trastuzumab, palbociclib and letrozole. Palbociclib is ad- ministered at 200 mg/day for 14 days of 21-day cycles. Trastuzumab and letrozole are administered at usual doses. As these combinations have not been tested in phase I trials, we incorporated a 2 cycles-safety run-in phase with the first 6 patients of each regimen. If the primary objective is to assess clinical efficacy measured as PFS at 6 months (PFS6). Assuming an increase of at least 20% in PFS6 by the addition of palbociclib +/- letrozole to trastuzumab, PFS6 should be ≥50% for a cohort to be successful and to proceed to stage 2. According to this, it will be necessary to include 15 patients in each cohort in stage 1. In stage 2, each cohort may continue recruitment for up to 46 patients. Translational research searching for predictive biomarkers will be implemented. To date, 43 patients, 13 in A and 13 in each B cohort, have been included in 14 sites across Spain. An independent safety data committee was held twice during the study. The
committee recommended that study continue enrollment as planned. The first stage efficacy analysis is intended for December 2017.

Clinical trial identification: NCT02448420

Legal entity responsible for the study: SOLTI Breast Cancer Research Group

Funding: Pfizer

Disclosure: All authors have declared no conflicts of interest.

322TIP

PYTHIA: A phase II study of palbociclib plus fulvestrant for pretreated patients with ER+/HER2- metastatic breast cancer

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Background: Palbociclib is an oral, potent, selective inhibitor of CDK4/6, blocking cell cycle progression from G1 into S phase. Preclinical data indicate that palbociclib has enhanced activity against luminal ER+ human breast cancer (BC) cell lines in vitro, combined with endocrine treatment. Randomized clinical trials showed significant PFS prolongation in patients with newly diagnosed and pretreated metastatic luminal BC, when palbociclib was combined with letrozole and fulvestrant respectively (PALOMA-1/2 and -3 trials). Predictive biomarkers for patient selection to receive palbociclib plus endocrine treatment are still missing.

Trial design: PYTHIA (IBCSG 53-14/BB 14-04) is a phase II, single-arm, multicenter, study of fulvestrant and palbociclib in postmenopausal women with ER+/HER2-, advanced BC, who progressed after prior endocrine treatment (1st or 2nd line; up to 1 line of prior chemotherapy allowed). Patients are enrolled concurrently in the AURORA program (NCT02302166), a longitudinal cohort study with extensive molecular characterization of matched primary-metastatic BC, and plasma samples. The primary endpoint is PFS, based on local assessment as per RECIST 1.1. Secondary endpoints include OS and tolerability, as well as disease control rate. Correlative objectives will assess the potential predictive value of: i) mutations and copy number alterations in a panel of cancer-related genes, ii) gene signatures inferred by RNA sequencing, iii) early FDG-PET/CT assessment performed for a subset of 30 patients, at baseline and Day 28, and iv) a serum thymidine kinase-1 (TK1) assay, performed at baseline, Day 14 and after Cycle 1. The sample size of 120 patients was selected to have 80% power to detect a HR of 2.0 for biomarker-positive patients, with 30-50% prevalence (two-sided α = 0.05). Enrollment opened in May 2016, with the target recruitment being 120 patients at 21 sites in Belgium, Italy and the UK.

Clinical trial identification: NCT02536742

Legal entity responsible for the study: International Breast Cancer Study Group (IBCSG)

Funding: Pfizer

Disclosure: All authors have declared no conflicts of interest.

323TIP

EarL-E1: A phase 3 study of ribociclib + endocrine therapy (ET) for adjuvant treatment of patients (pts) with hormone receptor-positive (HR+), human epididymal growth factor receptor 2-negative (HER2–) high-risk, early breast cancer (EBC)


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Background: Palbociclib added benefit of CDK4/6 inhibition when combined with anti-HER2 tx. The current study is designed to evaluate the added benefit of Palbociclib when given in combination with anti-HER2 and endocrine tx maintenance in the 1st line setting of metastatic HER2+ breast cancer.

The current study is designed to evaluate the added benefit of Palbociclib when given in combination with anti-HER2 and endocrine tx maintenance in the 1st line setting of metastatic HER2+ breast cancer.
Trial design: PATINA is an international, open-label, pivotal Phase III study. Primary objective is to demonstrate that the combination of Palbociclib with anti-HER2 plus endocrine tx is superior to anti-HER2 plus endocrine tx in prolonging PFS. Sample size is 496 pts. The study starts after completion of 6-8 cycles of chemotherapy-containing anti-HER2 tx for metastatic breast cancer in the 1st line setting. Pts are eligible provided they are without evidence of disease progression by local assessment (i.e. CR, PR or SD). To account for the need for less intense tx regimens for a subset of pts diagnosed with HER2+ ER+ disease, clinicians may recommend the combination of trastuzumab with either a taxane or vinorelbine prior to study initiation. Clinicians might also choose a non-Pertuzumab option for pts previously treated with pertuzumab in the neo(adjuvant) setting. Secondary objectives include measures of tumor control (OR, CBR, DOR), OS, safety and QOL. The translational science main objective is to compare PFS estimates according to PIK3CA mutation status assessed by cfDNA analysis. Endocrine tx options are AI or fulvestrant. Premenopausal pts must receive ovarian suppression. The study has a 90% power to detect a hazard ratio of 0.667 in favor of the palbociclib arm. Pts approached to participate in AFT-38 will be asked to indicate on the informed consent forms whether remaining biospecimens and clinical data from the control arm of the study can be shared with the Mastering Breast Cancer (MBC) Initiative. The overarching purpose of the MBC is to create a mechanism for understanding the natural history of metastatic breast cancer by cataloguing longitudinally studied tumor-specific markers and treatment effects.

Clinical trial identification: NCT02947685

Legal entity responsible for the study: Alliance Foundation Trials

Funding: Pfizer

Disclosure: C. Huang: Employee Pfizer Inc. M. Khoeler: Employee and shareholder Pfizer Inc. All other authors have declared no conflicts of interest.
Nivolumab (nivo) in combination with radiotherapy (RT) +/- Temozolomide (TMZ): Updated safety results from CheckMate 143 in pts with methylated or unmethylated newly diagnosed glioblastoma (GBM)

**Background:** Prognosis is poor for pts with GBM, as nearly all have recurrence after standard-of-care therapy. Nivo, a fully human IgG4 mAb inhibitor of the programmed death-1 receptor, is approved for the treatment of multiple cancers. Exploratory cohorts 1c and 1d of CheckMate 143 (NCT02017717) assessed the safety/tolerability of nivo in combination with RT ± TMZ in pts with newly diagnosed GBM.

**Methods:** In cohort 1c, pts received nivo 3 mg/kg Q2W ± concurrent TMZ (75 mg/m² daily) followed by adjuvant TMZ (150-200 mg/m², 5 days/28-day cycle for ≥6 cycles). In cohort 1d, pts received nivo 3 mg/kg Q2W ± standard RT without TMZ. All pts continued to receive nivo until confirmed progression/ unacceptable toxicity. Pts (n = 58) were initially assigned to 1c or 1d based on MGMT methylation status (1c, methylated or unmethylated; 1d, unmethylated). Following the initial evaluation, a second group of 55 pts with unmethylated MGMT were randomized 1:1 to 1c or 1d. Pooled safety data for all 113 pts are described here.

**Results:** Twelve pts with methylated and 43 pts with unmethylated MGMT were treated in 1c, and 58 pts with unmethylated MGMT were treated in 1d. Pts discontinued treatment in 1c (67% of pts in 1c and 1d; 83%) mostly due to radiographic progression (1c: 50% [methylated]; 37% [unmethylated]; 1d: 64%), study drug toxicity (8%, 9%, 10%), or pt decision (8%, 14%, 9%). AEs (all cause) are summarized in Table. The most common ≥ grade 3 AEs in any arm were headache (42%, 47%, 41%), rash (25%, 16%, 31%), and seizure (23%, 16%, 31%). No deaths due to study drug toxicity were reported.

**Conclusions:** Nivo with RT ± TMZ was well tolerated, with the frequency of neurological AEs consistent with that in other reports in this disease. These data support continued development of nivo ± RT ± TMZ in newly diagnosed GBM in the ongoing CheckMate 498 (NCT02617589) and CheckMate 548 (NCT02667587) trials.

**Clinical trial identification:** CA209143; Revised Protocol 04d, dated September 15, 2016

Legal entity responsible for the study: Bristol-Myers Squibb

Funding: Bristol-Myers Squibb


**Table: 3250 Summary of AEs (all cause)**

<table>
<thead>
<tr>
<th>Type of AE</th>
<th>Pts, n (%)</th>
<th>1c: Nivolumab + RT</th>
<th>1d: Nivolumab + TMZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate/Severe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>9 (7%)</td>
<td>22 (51%)</td>
<td>25 (43%)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (42%)</td>
<td>20 (47%)</td>
<td>24 (41%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (50%)</td>
<td>13 (30%)</td>
<td>10 (17%)</td>
</tr>
<tr>
<td>Seizure</td>
<td>3 (25%)</td>
<td>7 (16%)</td>
<td>18 (31%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (17%)</td>
<td>14 (33%)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>4 (33%)</td>
<td>4 (9%)</td>
<td>7 (12%)</td>
</tr>
<tr>
<td>Other neurological AEs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (17%)</td>
<td>3 (7%)</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>Visual field defect</td>
<td>2 (17%)</td>
<td>2 (5%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Cognitive disorder</td>
<td>2 (17%)</td>
<td>3 (7%)</td>
<td>5 (9%)</td>
</tr>
<tr>
<td>Other neurological AEs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash maculopapular</td>
<td>3 (25%)</td>
<td>2 (5%)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Bilirubin increased</td>
<td>1 (8%)</td>
<td>1 (2%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Cerebrospinal fluid leakage</td>
<td>0</td>
<td>3 (7%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Grade 3/4 AEs in ≥ 2 pts in any arm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocytes decreased</td>
<td>2 (17%)</td>
<td>5 (12%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>0</td>
<td>3 (7%)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>1 (8%)</td>
<td>2 (5%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Seizure</td>
<td>1 (8%)</td>
<td>3 (7%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Seizure</td>
<td>0</td>
<td>1 (2%)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>1 (8%)</td>
<td>0</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Muscular weakness</td>
<td>0</td>
<td>1 (2%)</td>
<td>3 (5%)</td>
</tr>
</tbody>
</table>

**Serious AEs in ≥ 2 pts in any arm**

<table>
<thead>
<tr>
<th>Type of AE</th>
<th>Pts, n (%)</th>
<th>1c: Nivolumab + RT</th>
<th>1d: Nivolumab + TMZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure</td>
<td>3 (25%)</td>
<td>4 (9%)</td>
<td>7 (12%)</td>
</tr>
<tr>
<td>Malignant neoplasm progression</td>
<td>2 (17%)</td>
<td>2 (5%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1 (8%)</td>
<td>3 (7%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Tumor flare</td>
<td>0</td>
<td>2 (5%)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>4 (9%)</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>
**Abstracts**

### 3260

The association of programmed death-ligand 1 (PD-L1), programmed cell death (PD-1), tumor infiltrating lymphocytes (TILs) and isocitrate dehydrogenase (IDH-1) mutation in glioblastoma multiforme (GBM)

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**Background:** PD-L1, PD-1 expression, TILs and IDH-1 mutation associations and their prognostic importance in GBM are planned to be assessed in the study.

**Methods:** GBM patients who were newly diagnosed and operated between February 2006 to February 2017 were included in the study. In initial tumor specimens PD-L1 PD-1 expression, C3D4(+) vs C3D4(-)/TIL vs IDH-1 mutation were assessed. For IDH-1 mutation analysis real time PCR technique was used, for PD-L1 and PD-1 assessment immunohistochemistry was performed by Ventana® antibody (clone SP263, ROCHE). For PD-1, PD-L1, C3D4, C3M TILs intensity was graded as low, moderate, dense and estimated in percentiles. The cut off value was defined as >5% for PD-L1, PD-1 positivity. Kaplan Meier, Cox regression tests and SPSS were used. Results: Ninety patients were included. The mean age was 57.12±(63,3%) patients were male. Forty eight (53,3%) patients were received chemotherapy and chemotherapy with temozolomide after operation. Two different staining patterns were diagnosed for PD-L1 expression as diffuse fibrillary (29,32,2%) and membrane staining (15,16,7%). Thirty (33%) patients have IDH-1 mutation. TILs were seen intensely in the perivascular field, which is rarely found in the intratumoral area and in that TILs, PD-1 staining grade was dense. We also observed a positive correlation between the density of TILs in the intratumoral/perivascular fields and the percentages of PD-L1 positivity (p<0,01), r=0,46. The intensity of both TILs in perivascular areas were significantly lower in PD-L1(-) tumors than in PD-L1(+) tumors (p<0,01). No significant correlation was found between TILs, PD-1 and TILs. We didn’t find any significant effect of age, sex, PD-L1 positivity and IDH-1 mutation status on survival. (log rank 0,03,078, 0,13, 0,64 respectively.) Presence of dense intratumoral PD-1(+)TILs and dense membranous PD-L1 staining were found as positive; advanced age was found as negative independent prognostic factors by multivariate analysis.

**Conclusions:** Staining pattern of PD-L1 and the density of PD-1 positivity in TILs may be a prognostic importance in GBM.

Legal entity responsible for the study: Didem Sener Dede

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Background: Low grade glioma (LGG) is a heterogeneous disease. Recently, the 2016 WHO classification of brain tumors has underlined the role of genetic and molecular features. Molecular astrocytomas have been defined as grade II tumors with IDH mutation and without 1p19q codeletion.

Methods: We evaluated 213 consecutive patients with LGG who received surgery or biopsy and had adequate tissue to assess molecular characterization. IDH mutations were assessed by immunohistochemistry (IHC) and next generation sequencing (NGS) in IHC negative cases. MGMT methylation status was assessed by polymerase chain reaction (PCR) and 1p19q deletion was assessed by fluorescence in situ hybridization (FISH).

Results: 198 patients (93.0%) showed IDH-mutation. Ninety patients (49.2%) were 1p19q non codeleted (molecular astrocytomas). The median follow up was 98.3 months. Median age was 36 (range: 18-69), 11 patients (12.2%) underwent biopsy, 48 (22.7%) patients were treated with post-surgical treatments and 31 patients (34.4%) received post-surgical treatments (12 months). At time of analysis no significant differences in OS were available.

Conclusions: IDH mutation is an independent prognostic factor for GB patient treated initially with standard therapy and with other therapies at recurrence.
immune checkpoint inhibitors is PD-L1 expression status and this can change over time with the effect of therapies like chemotherapy and radiotherapy. The aim of this study is to determine whether PD-L1 expression status changes in recurrent gliomas after chemoradiotherapy and the impact of this change on survival.

Methods: PD-L1 expression of 29 patients was evaluated by an expert pathologist with immunohistochemistry. PD-L1 positivity was defined as expression in ≥ 1% of tumor cells. Change in PD-L1 expression status was defined as an absolute 5% difference between two resections.

Results: Of the 29 patients, 15 patients (51.7%) had PD-L1 expression in ≥ 1% of tumor cells and 7 patients (24.1%) had PD-L1 expression in ≥ 10% of tumor cells at diagnosis. Median survival of patients with baseline PD-L1 <10% was 26 months, and in patients with PD-L1 ≥10% was 18 mo (P = 0.063). The PD-L1 status did not change in 17 patients (58.6%). 8 patients had PD-L1 negative tumors both at diagnosis and at recurrence, while 9 patients had PD-L1 positive tumors both at diagnosis and at recurrence. In 6 patients (20.7%) a negative to positive switch and in 5 patients (20.7%) a positive to negative switch were seen. The change in PD-L1 status over time was not statistically significant. The change of PD-L1 over time did not influenced overall survival of the patients (P = 0.45).

Conclusions: The PD-L1 expression status changes in more than 40% of high grade glial tumors at recurrence after receiving chemotherapy and radiotherapy. So immune responsiveness of glial tumors can be modified by treatments. As the patients in this study did not receive immunotherapy after recurrence, the change in PD-L1 expression probably did not affect survival.

Legal entity responsible for the study: Basak Oyan, Seyma Eren, Oltan Sonmez

Funding: Yeditepe University Hospital

Disclosure: All authors have declared no conflicts of interest.

333PD Meta-analysis of the effect of rituximab in the treatment of primary central nervous system lymphoma

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Background: Primary central nervous system lymphoma (PCNSL) is a rare subtype of aggressive non-hodgkin lymphoma (NHL), and is most commonly of B cell phenotype. The standard treatment is not well established but high dose methotrexate is the most commonly used regimen. Intravenous rituximab (iv Rtx) treatment is integrated into the protocols for systemic B cell lymphomas. However there are mixed results with the use of Rtx. The aim of this meta-analysis is to investigate the role of iv Rtx in the treatment of PCNSL.

Methods: PubMed and EBSCOhost databases are searched for rituximab, primary central nervous lymphoma, rituximab, survival. Browsing databases was done in English.

Results: 580 patients were included to meta-analysis. Poolled hazard ratio showed that overall survival is correlated with iv Rtx (HR, 0.49; 95% CI, 0.36 - 0.68, p < 0.001). Poolled hazard ratio was calculated by using fixed effect model. The quality determinations of 7 studies were done by using Newcastle-Ottowa Scale. The studies were counted low quality with the score 1-3, average quality with the score 4-6, high quality with the score 7-9. Median score of the studies was calculated as 5.

Conclusions: In this meta-analysis, we showed that the addition of iv Rtx as part of a treatment protocol for PCNSL has a positive impact on survival.

Legal entity responsible for the study: Mustafa Yıldırım

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Background: Although temozolomide (TMZ) was known to induce thrombocytopenia with subsequent cycle delay, dose reduction and early treatment discontinuation in glioblastoma multiforme (GBM), no early predictive test of these side effects has been yet clearly established. In this context, our aim was to identify the best threshold of early platelet variation predicting TMZ-induced thrombocytopenia during the TMZ maintenance phase and to validate it in an independent series of GBM patients.

Methods: It was a retrospective trial including patients suffering from newly diagnosed GBM and treated with TMZ at 75 mg/m²/day concomitant to radiotherapy (RT) followed by TMZ maintenance, according to the Stupp protocol. In a training set, variations of platelet concentrations occurring from the first week to week 6 (ΔW6) were analyzed to select decrease during RT-TMZ associated with at least one clinically relevant TMZ-induced thrombocytopenia (≤100 G/l) in the maintenance phase. An independent validation cohort was used to validate the performance of the ΔW6 threshold.

Results: A total of 147 patients were included: 85 in the training set and 62 in the validation cohort. Twenty-seven patients (18%) experienced at least one TMZ-induced thrombocytopenia in the maintenance phase, respectively 14% and 13% patients (21%) in each cohort; and was the most frequent cause of TMZ schedule changes (49%, 30/61). A platelet decrease at W6 ≥ 35% (ΔW6 ≥ 35%) was identified as the best predictive variation of clinically induced thrombocytopenia with an AUC of 0.83, a sensitivity (Se) of 65% and a specificity (Sp) of 96%. In the validation set, a presence of a variation of clinically induced thrombocytopenia with an AUC of 0.83, a sensitivity (Se) of 77% [95% CI 66%-87%], Sp 73% [62%-84%], a Youden index of 65% and a specificity (Sp) of 96%. In the validation set, a presence of a variation of clinically induced thrombocytopenia with an AUC of 0.83, a sensitivity (Se) of 77% [95% CI 66%-87%], Sp 73% [62%-84%], a Youden index of 65% and a specificity (Sp) of 96%.

Conclusions: Our results showed that a platelet decrease at W6 ≥ 35% during the RT-TMZ phase may be an early, widely feasible and costless marker of clinically relevant platelet variation. Prospective studies are needed to evaluate the usefulness of this test for early TMZ schedule adaptation.

Legal entity responsible for the study: Cancer Center Henri Becquerel

Disclosure: All authors have declared no conflicts of interest.
The enhanced internalisation within GSCs and the cytotoxic effect of anti-cancer treatment with GNP treatment. Chit-GNPs were 15 nm in size, with a positive zeta potential and proved a superior cell effect was evaluated through the MTT cell viability test and confirmed with Trypan blue-based counting.

Results: GSCs proved to express stem-cell markers and were highly resistant to radiotherapy. The fabricated Chit-GNPs were characterized by UV-vis-NIR extinction spectroscopy, transmission electron microscopy and zeta potential measurements. The enhanced internalisation within GSCs and the cytotoxic effect of Chit-GNPs were evaluated relatively to that of citrate-capped gold nanoparticles (GNPs) of similar size. Cell lines were treated with increasing concentrations of GNP and Chit-GNPs and then irradiated with hypofractionated radiotherapy (3 consecutive fractions of 1, 2 Gy) and brachytherapy (one single fraction of 1 and 2 Gy). The effect was evaluated through the MTT cell viability test and confirmed with Trypan blue-based counting.

Conclusions: The enhanced internalisation within GSCs and the cytotoxic effect of Chit-GNPs make this compound a suitable backbone for drug delivery in glioblastoma treatment, particularly as it proved to have selective toxicity for cancer cells. Surprisingly, Chit-GNPs were highly cytotoxic to glioma cell lines irrespective of irradiation.

Legal entity responsible for the study: Iuliu Hatieganu University of Medicine and Pharmacy

Funding: UEFISCDI - PNII-TE-2014-4-0225 (ENERGY)

Disclosure: All authors have declared no conflicts of interest.

Background: Glioblastoma is a rapidly lethal cancer with a stringent need for new treatment strategies. In this study, we tested if chitosan-capped gold nanoparticles (Chit-GNPs) may overcome the limitations of drug concentrations by an increased cell internalisation in glioblastoma stem-like cells (GSCs) and if such GNPs could enhance the response to irradiation.

Methods: GSCs lines were isolated from glioblastoma tumor fragments and characterized with stemness and neural markers. Chitosan biopolymer was used as reducing and stabilizing agent to generate Chit-GNPs through an environmentally friendly synthesis procedure. The fabricated Chit-GNPs were characterized by UV-vis-NIR extinction spectroscopy, transmission electron microscopy and zeta potential measurements. GSCs and two normal cell lines were selected for in vitro investigations. The uptake and cytotoxicity of Chit-GNPs were evaluated relatively to that of citrate-capped gold nanoparticles (GNPs) using a similar procedure. GSCs lines were treated with increasing concentrations of GNP and Chit-GNP. Radiotherapy at the tested doses failed to give an additional anti-cancer effect when combined with GNP treatment.

Results: GSCs proved to express stem-cell markers and were highly resistant to radiotherapy. Chit-GNPs were 15 nm in size, with a positive zeta potential and proved a superior cell internalisation compared to simple GNPNS. Normal cell lines remained unaffected by GNP and Chit-GNPs. Radiotherapy at the tested doses failed to give an additional anti-cancer effect when combined with GNP treatment.

Conclusions: The enhanced internalisation within GSCs and the cytotoxic effect of Chit-GNPs make this compound a suitable backbone for drug delivery in glioblastoma treatment, particularly as it proved to have selective toxicity for cancer cells. Surprisingly, Chit-GNPs were highly cytotoxic to glioma cell lines irrespective of irradiation.

Legal entity responsible for the study: Iuliu Hatieganu University of Medicine and Pharmacy

Funding: UEFISCDI - PNII-TE-2014-4-0225 (ENERGY)

Disclosure: All authors have declared no conflicts of interest.

Background: Glioblastoma (GBM) is the most malignant brain tumour with poor prognosis and limited therapy effectiveness. Tumour hypoxia is considered as a main reason of GBM’s resistance to medical treatment. It seems that improvement of therapeutic response can be achieved by the combination of chemotherapeutics application with refinement of oxygenation status of tumour tissue. One of the novel anti-tumour compounds is isoformsucker derivative ZKK-3, which inhibits the activity of protein kinase D1 (PKD1). PKD1 promotes tumour growth and mediates the formation of mitochondrial reactive oxygen species (ROS). The aim of this study was to examine the impact of hyperbaric oxygenation (HBO) on the expression of PKD1 protein as well as its phosphorylation forms - pPKD1 (Ser 916) and pPKD1 (Ser 744/748) in glioma cells treated with ZKK-3 in vitro.

Methods: Human glioblastoma T98G cell line was cultured in medium supplemented with ZKK-3 and exposed to the various oxygen conditions: normoxia, hypoxia, HBO, doxorubicin, hypoxia/HBO. After 24 hours the cell line was washed. The level of tested proteins in obtained lysates was measured using Western Blot technique.

Results: Increasing concentration of ZKK-3 caused diminution of pPKD1 (Ser 916) and pPKD1 (Ser 744/748) levels in all tested oxygen conditions. Comparison of hypoxia and HBO conditions showed that hypoxic conditions resulted in enhancement of expressions of all PKD1 forms. Moreover, in groups preincubated in hypoxia conditions the levels of tested proteins were also markedly elevated after hyperoxic oxygenation (hypoxia/HBO) in comparison to the double hypoxia groups.
Conclusions: Increase of PKD1 protein expression as well as its phosphorylated forms evidenced that HBO application resulted in enhancement of oxidative stress in 198G cell line in vitro. This combined with ZEK-3 ability to inhibit activities of those kinases gives ground to consider ZEK-3/HBO therapy as a promising therapeutic strategy for patients with malignant gliomas. Acknowledgement: The research was supported by KNOW-MMRC project and Foundation for the Development of Diagnostic and Therapy.

Legal entity responsible for the study: Mossakowski Medical Research Centre Polish Academy of Sciences

Funding: The research was supported by KNOW-MMRC project and Foundation for the Development of Diagnostic and Therapy.

Disclosure: All authors have declared no conflicts of interest.

Table 343P

<table>
<thead>
<tr>
<th>Variable</th>
<th>OS (months) P</th>
<th>PFS (months) P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDH mutation 187.2 vs 32.2 0.001 50.8 vs 16.5 &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1p19q codelation 189.4 vs 164.0 0.015 57.1 vs 41.1 0.031</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MGMT methylation 211.0 vs 148.7 0.013 56.0 vs 44.3 0.024</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery (complete vs biopsy) 211.0 vs 83.0 0.038 52.9 vs 40.0 0.011</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: The definition of LGG outcome is complex. Both clinical and molecular factors are needed to determine prognosis and treatment strategies.

Legal entity responsible for the study: N/A

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Background: Glioblastoma is the most common primary brain tumor. The current standard therapy for patients with glioblastoma is surgery and combination of radiotherapy with temozolomide chemotherapy. However, the prognosis is still very poor. Much research has been done to improve patient outcomes in glioblastoma. Recently, immunotherapy with immune checkpoint inhibitors, such as ipilimumab, nivolumab, and pembrolizumab shows great clinical improvements in other advanced tumors, which make immunotherapy an attractive strategy in glioblastoma treatment.

Methods: The expression of PD-L1 was determined by flow cytometry. The concentration of adriamycin was determined by CCK-8 assay depending on the inhibition rate of U251 cells, which was set to less than 50% (IC50). After treatment with different concentrations of adriamycin, cell proliferation of T lymphocytes was detected by CCK-8 method, cell apoptosis of T lymphocytes and PD-L1 expression were analysed by flow cytometry. Treated with different concentrations of adriamycin alone or in combination with PD-L1 inhibitor, U251 cells and T lymphocyte proliferation in co-culture were determined by CCK-8 assay.

Results: The expression of PD-L1 was nearly 70%. The IC50 of adriamycin was 4.29mg/L. Adriamycin could enhance the proliferation of T lymphocytes when concentration was less than 4.29mg/L and could up-regulate the expression of PD-L1. Adriamycin (4.28mg/L) combined with immunotherapy (PD-L1 inhibitor 1.5mg/L) could inhibit glioma cells growth obviously and the number of dead T lymphocytes in co-culture system was reduced.

Conclusions: Adriamycin combined with immunotherapy (PD-L1 inhibitor) is a promising strategy for glioma treatment and our research provides theoretical basis for combination of adriamycin and immunotherapy in glioma treatment.

Legal entity responsible for the study: Shiyu Zheng

Funding: Laboratory for Experimental Medicine and Surgery of Southeast University

Disclosure: All authors have declared no conflicts of interest.
Background: The NLR is a marker of systemic inflammatory response and elevated levels have been associated with aggressive disease and poorer outcome in multiple cancers, including prostate, lung and colon cancer. In pts with GBM, elevated NLR prior to any initial therapy is predictive for worse outcomes. For pts with refractory PMBT, the role of NLR is uncertain. We aimed to assess the prognostic impact of NLR, and the impact of corticosteroids (CCS) in pts with PMBT referred for consideration of Ph1 trial.

Methods: Retrospective data were collected on treatment (tx) and tumour characteristics of pts with PMBT referred for consideration of Ph1 trial participation between 06/2004-09/2016. Survival analyses were performed using the Kaplan-Meier method, Cox proportional hazards model, chi-square test was used to measure associations between categorical variables.

Results: 100 pts with advanced, refractory PMBT were referred. All pts had received at least one line of prior tx; median no. of prior systemic therapies was 2; 76% had GBM; 63% required CCS on first assessment. Use of CCS was associated with shorter disease-free survival (HR 1.93, 95% CI 1.21-3.06, p = 0.005) and shorter overall survival (OS in both univariate (HR 2.33, 95% CI 1.44-3.77, p = 0.001) and multivariate analysis [MVA] (HR 1.84, 95% CI 1.03-3.24, p = 0.034). Pts with NLR >4 were more likely to require CCS compared to pts with an NLR <4 (81% vs 38%). NLR >4 was associated with poorer outcomes in all models (OS, MVA, HR 1.73, 95% CI 1.02-2.94, p-value 0.043). Use of CCS did not modify the association between NLR and outcomes. Patients with an NLR >4 and requiring CCS had the poorest outcome (p = 0.0364); median OS (mOS) for pts with NLR >4 on CCS was 4 months (m) (SE 0.29, 95% CI 3.29-5.42), vs 19 m noOS for pts not taking CCS (SE 0.81, 95% CI 3.68-not reached).

Conclusions: In our advanced PMBT cohort, elevated NLR >4 remained an independent prognostic indicator for poor outcome, independent of the use of CCS. Pts with elevated NLR requiring CCS demonstrated the worst outcomes – a reminder of the potential relevance of host immunity in PMBT.

Legal entity responsible for the study: Royal Marsden Hospital

Funding: None


All other authors have declared no conflicts of interest.

Table: 348P Results of univariate analysis

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>mOS</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>methylated male</td>
<td>31</td>
<td>16.3</td>
<td>9.2-23.4</td>
</tr>
<tr>
<td>unmethylated male</td>
<td>41</td>
<td>15.6</td>
<td>11.8-19.5</td>
</tr>
<tr>
<td>methylated female</td>
<td>26</td>
<td>nr</td>
<td></td>
</tr>
<tr>
<td>unmethylated female</td>
<td>21</td>
<td>17.0</td>
<td>11.8-22.2</td>
</tr>
<tr>
<td>total</td>
<td>119</td>
<td>17.0</td>
<td>15.2-18.9</td>
</tr>
</tbody>
</table>

Conclusions: The median overall survival is consistently higher for female pts with methylated MGMT, treated with temozolomide concurrent with and adjuvant to radiotherapy. When considered simultaneously with MGMT methylation status, gender might impact on clinical outcome and should be considered as a prognostic factor.

Legal entity responsible for the study: N/A

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Objectives: To determine the prognostic impact of neutrophil-to-lymphocyte ratio (NLR) in patients (pts) with recurrent primary malignant brain tumours (PMBT) in phase I (Ph1) trials: The Royal Marsden (IMHM) Experience

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1Oncology, Institute of Cancer Research Royal Marsden Hospital, Sutton, UK, 2Radiology, The Royal Marsden NHS Foundation Trust, London, UK

Background: The NLR is a marker of systemic inflammatory response and elevated levels have been associated with aggressive disease and poorer outcome in multiple cancers, including prostate, lung and colon cancer. In pts with GBM, elevated NLR prior to any initial therapy is predictive for worse outcomes. For pts with refractory PMBT, the role of NLR is uncertain. We aimed to assess the prognostic impact of NLR, and the impact of corticosteroids (CCS) in pts with PMBT referred for consideration of Ph1 trial.

Methods: Retrospective data were collected on treatment (tx) and tumour characteristics of pts with PMBT referred for consideration of Ph1 trial participation between 06/2004-09/2016. Survival analyses were performed using the Kaplan-Meier method, Cox proportional hazards model, chi-square test was used to measure associations between categorical variables.

Results: 100 pts with advanced, refractory PMBT were referred. All pts had received at least one line of prior tx; median no. of prior systemic therapies was 2; 76% had GBM; 63% required CCS on first assessment. Use of CCS was associated with shorter disease-free survival (HR 1.93, 95% CI 1.21-3.06, p = 0.005) and shorter overall survival (OS in both univariate (HR 2.33, 95% CI 1.44-3.77, p = 0.001) and multivariate analysis [MVA] (HR 1.84, 95% CI 1.03-3.24, p = 0.034). Pts with NLR >4 were more likely to require CCS compared to pts with an NLR <4 (81% vs 38%). NLR >4 was associated with poorer outcomes in all models (OS, MVA, HR 1.73, 95% CI 1.02-2.94, p-value 0.043). Use of CCS did not modify the association between NLR and outcomes. Patients with an NLR >4 and requiring CCS had the poorest outcome (p = 0.0364); median OS (mOS) for pts with NLR >4 on CCS was 4 months (m) (SE 0.29, 95% CI 3.29-5.42), vs 19 m noOS for pts not taking CCS (SE 0.81, 95% CI 3.68-not reached).

Conclusions: In our advanced PMBT cohort, elevated NLR >4 remained an independent prognostic indicator for poor outcome, independent of the use of CCS. Pts with elevated NLR requiring CCS demonstrated the worst outcomes – a reminder of the potential relevance of host immunity in PMBT.

Legal entity responsible for the study: Royal Marsden Hospital

Funding: None


All other authors have declared no conflicts of interest.
Conclusions: Quality of life analyses are ongoing. Given the cost of BEV, these results have important implications for value in cancer care.

Methods: We retrospectively analysed data from the prospective database of the neuro-oncology centre in Ireland. All patients who received BEV at the time of progression for histologically-proven de novo GBM from 2010 to 2016 were included. At our institution there is variable practice between Neuro-Oncologists in terms of BEV dosing schedule - standard BEV dosing (10mg/kg q 2wks or 15mg/kg q 3wks) vs. reduced-intensity BEV (5mg/kg q 2wks or 7.5mg/kg q 3wks). Using the Kaplan-Meier method, we assessed OS in the entire cohort and by BEV dosing schedule.

Results: In total, 118 patients received BEV for progressive GBM. Median OS was 5.6 months for the entire population (range: 0.5-42 months) and OS was 45%, 18% and 2% at 6-, 12- and 24-months, respectively. Patient characteristics by BEV dosing schedule were similar (Table). Median OS was similar in the reduced intensity BEV group (N = 49) at 5.5 months and the standard-dose group (N = 69) at 5.6 months, p=0.55. Quality of life analyses are ongoing.

Table: 349P

<table>
<thead>
<tr>
<th>Dose BEV</th>
<th>Standard</th>
<th>Reduced</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>N = 69</td>
<td>N = 49</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>45 (65%)</td>
<td>32 (65%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Female</td>
<td>24 (35%)</td>
<td>17 (35%)</td>
<td></td>
</tr>
<tr>
<td>AGE</td>
<td>N = 69</td>
<td>N = 49</td>
<td></td>
</tr>
<tr>
<td>&lt; 45 years</td>
<td>10 (14.5%)</td>
<td>8 (16%)</td>
<td>0.92</td>
</tr>
<tr>
<td>45-65 years</td>
<td>42 (60.9%)</td>
<td>28 (57%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 65 years</td>
<td>17 (24.6%)</td>
<td>13 (27%)</td>
<td></td>
</tr>
<tr>
<td>MGMT</td>
<td>N = 69</td>
<td>N = 49</td>
<td></td>
</tr>
<tr>
<td>Methylated</td>
<td>20 (40%)</td>
<td>17 (47%)</td>
<td>0.50</td>
</tr>
<tr>
<td>Unmethylated</td>
<td>30 (60%)</td>
<td>19 (53%)</td>
<td></td>
</tr>
<tr>
<td>Time from Diagnosis to BEV start</td>
<td>N = 69</td>
<td>N = 49</td>
<td>0.55</td>
</tr>
<tr>
<td>&lt; 12 months</td>
<td>36 (52%)</td>
<td>24 (49%)</td>
<td></td>
</tr>
<tr>
<td>12-18 Months</td>
<td>16 (23%)</td>
<td>12 (24%)</td>
<td>0.94</td>
</tr>
<tr>
<td>&gt; 18 months</td>
<td>17 (25%)</td>
<td>13 (27%)</td>
<td></td>
</tr>
<tr>
<td>Median Overall</td>
<td>5.6 Months</td>
<td>5.5 Months</td>
<td>0.55</td>
</tr>
<tr>
<td>Survival post BEV</td>
<td></td>
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</tbody>
</table>

Conclusions: In this large heterogeneous cohort of patients, OS was similar in patients who received standard or reduced intensity BEV for treatment of progressive GBM. Given the cost of BEV, these results have important implications for value in cancer care.

Legal entity responsible for the study: Cancer Clinical Trials Unit (CCTU), Beaumont Hospital, Dublin, Ireland
Funding: None
Disclosure: All authors have declared no conflicts of interest.

Table: 350P

<table>
<thead>
<tr>
<th></th>
<th>PCV</th>
<th>TMZ</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>57 (range 29-71)</td>
<td>63 (range 34-80)</td>
<td>0.119</td>
</tr>
<tr>
<td>Excision</td>
<td></td>
<td></td>
<td>0.613</td>
</tr>
<tr>
<td>Debulking</td>
<td>25 (80.6%)</td>
<td>13 (86.7%)</td>
<td></td>
</tr>
<tr>
<td>Biopsy</td>
<td>6 (19.4%)</td>
<td>2 (19.4%)</td>
<td></td>
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<tr>
<td>Radiological Appearance</td>
<td></td>
<td></td>
<td>0.182</td>
</tr>
<tr>
<td>Single</td>
<td>24 (77.4%)</td>
<td>14 (93.3%)</td>
<td></td>
</tr>
<tr>
<td>Multifocal</td>
<td>7 (22.6%)</td>
<td>16 (6.7%)</td>
<td></td>
</tr>
<tr>
<td>Adjuvant Treatment</td>
<td></td>
<td></td>
<td>0.816</td>
</tr>
<tr>
<td>Radical chemo-RT</td>
<td>25 (80.6%)</td>
<td>13 (86.7%)</td>
<td></td>
</tr>
<tr>
<td>Radical RT alone</td>
<td>26 (5%)</td>
<td>16 (6.7%)</td>
<td></td>
</tr>
<tr>
<td>Palliative RT</td>
<td>4 (12.9%)</td>
<td>16 (6.7%)</td>
<td></td>
</tr>
<tr>
<td>Adjuvant treatment completed within 6 months</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>1 (3%)</td>
<td></td>
<td>11 (73%)</td>
<td></td>
</tr>
<tr>
<td>Median time to progression after “rst-line” (months)</td>
<td>1.2 (range 0.7-11.03)</td>
<td>9.8 (range 1-24.3)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

350P An individualized approach to second-line systemic anti-cancer therapy for glioblastoma

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1Oncology Department, Norwich and Norwich University Hospital, Norwich, UK
2Oncology Department, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

Background: The optimal second-line systemic anti-cancer therapy (SACT) for recurrent inoperable glioblastoma (GBM) is not known. Generally, patients with a recurrence within 6 months of adjuvant temozolomide (TMZ) are treated with procarbazine/lomustine/vincristine (PCV) regimen and those with a recurrence at least 6 months after completion of TMZ are re-challenged with TMZ (rTMZ). The aim of this study is to evaluate the clinical outcomes of this individualized approach.

Methods: We treated 46 patients with second-line SACT for recurrent GB between 2009 and 2015. The Response Assessment in Neuro-Oncology (RANO) criteria were used to assess treatment response. The Kaplan-Meier method was used to calculate survival. Patient- and disease-related characteristics between the groups were compared using the Fisher exact test.

Results: 31 patients received PCV and 15 patients received rTMZ (Table). The median progression-free survival (PFS) (3.4 months each) and overall survival (OS) (5.2 vs 5.3 months p = 0.482) from the start of second-line SACT were similar for both groups. Compared with the PCV group, the median PFS (19.6 months vs. 8.7 months, p = 0.001) and OS (28 months vs. 13.7 months, p = 0.001) calculated from the date of diagnosis were better for the rTMZ group. Toxicity was acceptable in both treatment groups.

Conclusions: As the individualized approach of second-line SACT in recurrent GB leads to similar survival. Patients who recur more than 6 months after completion of primary chemo-radiotherapy generally have a better survival.

Legal entity responsible for the study: Department of Radiation Oncology, Norfolk & Norwich University NHS Foundation Trust
Funding: None
Disclosure: All authors have declared no conflicts of interest.

351P Leviteracetam offers a survival advantage in patients with epilepsy related to MGMT unmethylated glioblastoma

L. Rojas1, A. Ruiz-Patiño2, A.F. Cardona3, O. Arrieta4, Z. Zatarain-Barrón4
1School of Medicine, Pontificia Universidad Javeriana, Bogotá, Colombia, 2School of Medicine, Hospital Universitario San Ignacio-Pontificia Universidad Javeriana, Bogotá, Colombia, 3Clinical Oncology, Foundation for Clinical and Applied Cancer Research FICMAC, Bogotá, Colombia, 4Thoracic Oncology Unit and Laboratory of Personalized Medicine, Instituto Nacional de Cancerología - Mexico, Ciudad De México, Mexico

Background: Epilepsy is a common symptom in patients with glioblastoma (GB). Leviteracetam (LEV), an antiepileptic drug (AED), enhances MGMT inhibition and...
reduces chemotherapy mediated neuronal toxicity, offering a theoretical benefit over other AEDs.

Methods: 213 Hispanic patients were included. All patients underwent surgery (if feasible) followed by chemoradiation based on temozolomide. Type of AED was selected under treating physician discretion. Recorded variables included demographics, AED, dosage, MGMT status, performance status (PS) and type of surgical intervention. The relationship between overall survival (OS), AED and MGMT methylation status was explored.

Results: Mean age was 53-yr (SD +/-14.7), 56.8% were male, 73% presented with epilepsy after diagnosis and 50.7% harbored methylated MGMT (metMGMT). 41% were treated with LEV, 26% were given another AED and 35% did not require any AED. AED indication was not associated with age (p = 0.087), PS (p = 0.78) or anatomic tumor site (p = 0.34) or MGMT status (p = 0.98). Median OS was 25.8 months (95% CI 21.6-31.5), 27.9 months (95% CI 23.8-33.7) for those with metMGMT, and 11.83 months (95% CI 6.3-11.8) for non-met-methylated (p < 0.001). Patients who achieved seizure control and had metMGMT reached an OS of 22.5 months (95% CI 17.5-27.2) compared to 5.3 months (95% CI 4.3-6.2) for non-met-MGMT and seizure free patients (p < 0.001). Within the non-methylated groups, LEV in non-metMGMT offered an OS advantage to other AED and non-AED treated patients (p = 0.001) whereas this benefit was not observed in metMGMT (p = 0.639).

Conclusions: Retrospective analysis of this cohort suggests that LEV modifies OS in non-metMGMT Gb patients making it comparable to those with metMGMT. Further validation of this data in clinical trials is warranted.

Legal entity responsible for the study: Leonardo Rojas

Funding: None

Disclosure: All authors have declared no conflicts of interest.

352P The prognostic role of indicators of systemic inflammatory response in patients with glioblastoma

V. Kayas1, M. Yildirim1, G. Yazici1, A.Y. Yakub2, N. Orhan3, A. Guzel1
1Department of Radiation Oncology, Medstar Antalya Hospital, Antalya, Turkey, 2Internal Medicine, Bahcesehir Universities, Gaziantep, Turkey, 3Department of Radiation Oncology, Hacettepe University, Ankar, Turkey

Background: High grade gliomas, among which glioblastomas are the most frequently observed histologic subtype, are the most common primary brain tumors in adults. The standard treatment for glioblastoma consists of maximal safe resection, followed by concomitant chemoradiotherapy. It was reported that inflammatory response plays a major role in malignancy, including tumor progression. This study aimed to determine the prognostic role of the neutrophil to lymphocyte ratio (NLR) and the thrombocyte to lymphocyte ratio (PLR)—both indicators of systemic inflammatory response (SIR)—in patients with glioblastoma.

Methods: This study retrospectively evaluated 90 patients that were treated for glioblastoma.

Results: Median follow-up time was 11.3 months (range: 1-70 months). The 1-year and 2-year overall survival rates were 55.2% and 19.3%, respectively. Univariate analysis showed that there wasn’t a correlation between overall survival and gender (p = 0.184), comorbid diseases (p = 0.93), clinical presentation (p = 0.848), or tumor localization (p = 0.190). The prognostic factors that affected survival—other than SIR—were Eastern Cooperative Oncology Group (ECOG) performance status (p = 0.003), and tumor localization (p = 0.008). Multivariate analysis showed that overall survival was significantly correlated with SIR based on NLR (HR: 2.41), and ECOG performance status (HR: 1.53).

Conclusions: These findings confirm that the NLR value obtained from peripheral blood prior to treatment can be used as a prognostic factor in patients with glioblastoma. It is known that a high NLR value (NLR ≥ 5) is indicative of aggressive disease with decreased survival; therefore, aggressive treatment modalities can be offered to this selected patient population.

Legal entity responsible for the study: Mustafa Yildirim

Funding: None

Disclosure: All authors have declared no conflicts of interest.

353P Which patients with recurrent glioblastoma will require a second surgery during their treatment? A machine learning solution

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1School of Medicine, Hospital Universitario San Ignacio-Pontificia Universidad Javeriana, Bogotá, Colombia, 2Clinical Oncology, Foundation for Clinical and Applied Cancer Research FCMAC, Bogotá, Colombia, 3School of Medicine, Pontificia Universidad Javeriana, Bogotá, Colombia, 4Thoracic Oncology Unit and Laboratory of Personalized Medicine, Instituto Nacional de Cancerología - Mexico, Ciudad De Mexico, Mexico

Background: Deciding upon the therapeutic approach for patients with recurrent glioblastoma (Gb) is a challenge. Although a second surgery may provide effective palliation, it has yet to be established whether it prolongs survival and/or improves quality of life; previous reported data is scarce to demonstrate that reoperation is indicated for all patients with recurrence. The few studies investigating this issue are retrospective and have been conducted on small series with heterogeneous data sets. The aim of the present study was to analyze potential predictors of outcome in patients with recurrent Gb selected for second surgery.

Methods: A statistical learning model based on artificial neural networks was performed. 144 Hispanic patients with Gb were selected, included variables were age, performance status (PS), MGMT promoter methylation (MGMTmet), IDH1/2, and extent of previous surgical resection (ESR). The objective was to identify patients who were candidates for a second surgery considering multiple variable combination models. The overall survival (OS) 17 comparisons were made to identify the best model for later validation.

Results: 41 patients (49.7%) were female, median age was 52 years old (SD +/-14.3), 63 cases (43.8%) were older than 60 years, 125 (86.8%) had a Karnofsky Performance Index (KPS) ≥ 70, 73 (50.7%) had methylated MGMT and 124 (86.1%) underwent subtotal or total surgical resection. The best predictive variables for requiring a second surgery were age, PS, extent of surgical resection and MGMT metylation status. With an area under the curve of 0.984, combined age plus MGMTmet had a sensitivity of 78% and a specificity of 95%. Other models including MGMTmet + IDH1, age + KPS and age + KPS + ESR yielded an AUC of 0.806, 0.866, and 0.854, respectively. All differences were statistically significant with p value < 0.05.

Conclusions: The identification of patients who will require a second surgical intervention can be achieved, offering patients and clinicians an objective tool to plan and carry out the surgical therapy.

Legal entity responsible for the study: A

Funding: None

Disclosure: All authors have declared no conflicts of interest.

354P The prognostic role of age in salvage re-irradiation applied patients with recurrent glioblastoma: A meta-analysis

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1Faculty of Health Sciences, Istanbul Bilgi University, Istanbul, Turkey, 2Department of Radiation Oncology, Medstar Antalya Hospital, Antalya, Turkey, 3Department of Radiation Oncology, Hacettepe University, Ankar, Turkey, 4Department of Neurosurgery, Medicalpark Gaziantep Hospital, Gaziantep, Turkey

Background: Glioblastoma is the most common primary malignant brain tumor in adults. Despite of postoperative adjuvant therapy, glioblastoma recurs in almost all the patients. After recurrence, chemotherapy, carmustine wafer intended for lesions, usage of anti-VEGF, re-operation, re-irradiation are the existent salvage therapy options. In this meta-analysis, the prognostic role of age in salvage re-irradiation applied patients with recurrence glioblastoma was analyzed.

Methods: PubMed and EBSCOhost databases are searched for malignant glioma, high-grade glioma, recurrence, survival, re-irradiation, re-irradiation. Browsing databases was done in English.

Results: 1588 patients were included to meta-analysis. Pooled hazard ratio showed that overall survival is correlated with re-operation (HR, 1.042; 95% CI, 1.012-1.073, p = 0.006). Pooled hazard ratio was calculated by using fixed effect model. The quality determinations of 4 studies were done by using Newcastle-Ottawa Scale. The studies were counted low quality with the score 1-3, average quality with the score 4-6, high quality with the score 7-9. Median score of the studies was calculated as 5.

Conclusions: In this meta-analysis, we showed that for re-irradiation treatment, which is a salvage therapy option for recurrent glioblastoma, the age is an important prognostic factor.

Legal entity responsible for the study: Mustafa Yildirim

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Temozolomide combined with fractionated stereotactic radiotherapy for large brain metastases: A propensity-matched Study

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Background: This study was conducted to investigate the efficacy and safety of temozolomide (TMZ) with fractionated stereotactic radiotherapy (FSRT) for large brain metastases (BMs).

Methods: From 2009 to 2016, 72 patients (pts) with large BMs (diameter >3 cm or volume >6 cm³) undergoing concurrent TMZ and FSRT (Group A, n = 36) or FSRT alone (Group B, n = 36) were compared by using the propensity score matching method at the ratio of 1:1. Finally, 27 pts of each group were matched. FSRT was given by S2.5 Gy/3.5-4 Gy/13-15 Fr, while TMZ was given by 75 mg/m² concurrently. The disease control rate (DCR, CR+PR+SD) was assessed after 2-3 months from treatment. Toxicity was recorded according to CTCAE v4.0. Local control (LC), intracranial progression-free survival (IPFS), progression-free survival (PFS) and overall survival (OS) were assessed with Kaplan-Meier method and log-rank test.

Results: The median GTV of Group A and B were 19.7 cc (6.0-142.81 cc) and 15.7 cc (6.27-62.35 cc), respectively. During treatment, more lesions in Group A shrink greatly and got re-contoured (39 VS 29, p = 0.005), and the median GTV shrinkage rate was 30.5% versus (VS) 23.1%. After 2-3 months of treatment, the DCR was 97.4% (37/38) in Group A and 85.3% (29/34) in Group B (p = 0.046). The median follow-up time was 20.6 months. Before matching, the LC (p = 0.037) and PFS (p = 0.025) of Group A were significantly greater than Group B. IPFS (p = 0.059) and OS (p = 0.059) were marginally longer in Group A. After matching, the median PFS time and 1-year PFS rate of Group A were significantly greater than Group B (12.7 vs 3.3 months and 55.2% vs 26.4%, respectively, p = 0.041). The rate of intracranial progression death of Group A was significantly lower (18.2% VS 45.8%, p = 0.04). Both overall survival time and IPFS were also marginally longer in Group A (MST: 23.7 vs 12.75 months, p = 0.064; 1-IPFS: 61.6% VS 40.7%, p = 0.069), while there was no significant difference in 1-y OS (89.8% VS 84.2%, p = 0.23). There was no severe toxicity in both groups (p = 0.062).

Conclusions: The addition of TMZ to FSRT shows advantages in accelerating the shrinkage of large BMs and might improve intracranial control and overall survival, with no increase of toxicities. Further studies with large sample sizes are warranted.

Clinical trial identification: NCT02604106

Legal entity responsible for the study: Cancer Hospital, Chinese Academy of Medical Sciences

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Worsening of quality of life (QoL), cognitive functions (CF) and psychological status (PSY) can predict radiologic progressive disease (RPD) in glioblastoma (GBM) patients (PTS) treated with radiation therapy (RT) and temozolomide (TMZ): A mono-institutional prospective study

E. Beretti1, G. Lombardi1, P. Del Bianco2, S. Dal Pos3, F. Berti4, L. Bellù5, A. Pambukçu1, V. Zagone6
1Clinical and Experimental Department, Medical Oncology I, Veneto Institute of Oncology, Padua, Italy; 2Clinical Trials and Bioassays Unit, and Molecular Immunology and Oncology Unit, Veneto Institute of Oncology, Padua, Italy; 3Neuroanatomy Laboratory, University Hospital of Padua, Padua, Italy; 4Radiation Therapy and Nuclear Medicine Unit, Veneto Institute of Oncology, Padua, Italy

Background: Almost all PTS with GBM treated with RT and TMZ relapse during or after treatment. We performed a prospective study to assess if deterioration of QoL, CF and PSY is a predictor of RPD.

Methods: PTS with newly histologically diagnosed GBM treated with RT and TMZ as first-line therapy and KPS ≥ 60 were enrolled. PTS received TMZ for 12 cycles or until unacceptable toxicity or progressive disease. All questionnaires were given to PTS for self-assessment before performing MRI. Macdonald criteria were used for radiological evaluation. We assessed QoL, CF and PSY before starting treatment, at the end of RT, and every 3 months until 9 months after the end of RT using EORTC-C30, BN-20, MMSE and HADQ questionnaires. Brain MRI were performed at the same timepoints.

Results: We prospectively enrolled 111 consecutive PTS at our oncological center, Veneto Institute of Oncology, between January 2013 and December 2015. Median age was 59.69 PTS were male and 36 PTS aged ≥65. PTS showed a RPD reported lower physical functioning (p = 0.018), minor role function (p = 0.0007) and a lower global health status (p = 0.01) than patients without RPD. In addition, they reported greater uncertainty in the future (p = 0.007), increased drowsiness (p = 0.013), increased itchy skin (p = 0.005) and greater weakness in the leg (p = 0.027) compared to PTS without RPD. PTS with RPD were more anxious (p = 0.0021) and depressed (p = 0.0001) than PTS without RPD. The two groups significantly differed in CF (p = 0.0007), especially 1 and 6 months after RT, with worse results in the MMSE for PTS with RPD.

Conclusions: Worsening of QoL, CF and PSY can predict RPD in GBM PTS treated with RT and TMZ.

Legal entity responsible for the study: Veneto Institute of Oncology

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Dose distribution after tumor cavity injection in brain glioma patients

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Background: The local delivery of drug into brain has not been widely used because the unpredictable dose distribution and dose-toxicity effects that drug may carry. This study is to investigate the efficacy of drug delivery by intra-cerebral injection.

Methods: 3 patients with deep-seated glioma underwent stereotactic biopsy and Ommaya reservoir implantation. Radioactive agent (131I-chTNT) was injected at a dose of (0.8mcCi/cm³) through Ommaya reservoir. Patients were carefully observed and Post-operative PET was performed to reveal the body distribution of 131I and evaluate the distribution of drugs in whole body.

Results: After the intratumoral injection, most of the drug stayed in the brain tumor and decayed gradually for more than 4 weeks. Although the accumulation of 131I was also found in thyroid and urinary system as well as stomach and large intestine, it dis appeared within 2 weeks while strong radioactivity was still seen in the brain tumor.

Conclusions: These images demonstrated excellent localization of the radiolabel in the tumor with little diffusion over time. Intra-tumoral injection of chemical or radioactive drugs is recommendable in the local treatment.

Legal entity responsible for the study: Ming Zhao

Funding: Beijing Capital Developmental Fund (2014-2-5021)

Disclosure: All authors have declared no conflicts of interest.

Retrospective analysis to ascertain whether thromboembolic events, patient gender and tumour size have prognostic implications for glioblastoma multiforme

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Background: Glioblastoma multiforme is a rare grade 4 incurable brain malignancy. Well established prognostic indicators for this disease include performance status, age and cognitive function at diagnosis. Presenting with a seizure is also known to predict a better prognosis. Patient gender, tumour size and thromboembolic events have not been previously known to have prognostic significance. The rationale of this study is to identify alternative features which could be used as additional prognostic indicators.

Methods: We conducted a retrospective analysis of all patients diagnosed with glioblastoma multiforme at Derriford Hospital, Plymouth, UK between 2009 and 2016. We analysed factors such as survival time since diagnosis, patient demographics, tumour size at diagnosis, performance status at diagnosis, presenting symptom, treatment undergone and the occurrence of venous thromboembolic events since diagnosis.

Results: 92 patients were included. The occurrence of venous thromboembolism had no impact on survival time (p = 0.386). Male sex appeared to predict a better prognosis than female sex, however, this did not quite achieve statistical significance with a p value of 0.09. Cox regression analysis revealed tumour size on diagnosis to be significantly negatively correlated with survival time, with a p value of 0.012. Our analysis agreed with previous findings that multifocal disease and increased age are poor prognostic indicators, and presenting with seizures is a good prognostic indicator. Patients who underwent radical debulking surgery followed by concomitant chemoradiation had a significantly longer survival time than patients who had best supportive care alone.

Conclusions: Our analysis has shown that increasing tumour size is negatively correlated with survival duration. This link has not been previously established. Female sex may also be a poor prognostic indicator, but our data did not achieve statistical significance so further research investigating this potential link may be warranted. Venous thromboembolic events had no impact on prognosis.

Legal entity responsible for the study: Research Office, Plymouth Hospitals NHS Trust

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Background: Medulloblastoma is the most common type of childhood brain tumors. We conducted Korea’s nation-wide protocol-based treatment for medulloblastoma, and adopted tandem high dose chemotherapy for high risk disease. Here we present the result of treatment in Yonsei Cancer Center using the protocol and elucidate dose-response relationship.

Methods: The patient diagnosed and treated in Yonsei Cancer Center were reviewed retrospectively, from 2006 to 2015. We excluded the patients less than 3 years old and over 30 years old. Dose intensity (DI) was calculated as actual dose level/planned dose level divided by chemotherapy treatment duration. Ind-DI was defined as induction chemotherapy DI and HDCT-DI as high dose chemotherapy DI. The protocol was composed of 2 cycles of neoadjuvant chemotherapy and 32.4Gy of craniospinal radiotherapy (CSRT) and 30.4 Gy of total tumor dose. After the radiotherapy, 4 cycles of chemotherapy and tandem high dose chemotherapy was done.

Results: Among total 39 patients, 16 were standard risk (SR) and 23 were high risk (HR). The 5 year overall survival (OS) was 92% for SR, and 67% for HR. Disease specific survival (DSS) for HR was 75%, and therefore 8% was treatment related mortality (TRM). The TRM in stage II and M1 status was not statistically different in HR. The ind-DI did not affect in SR for OS and SR. HR was strongly correlated with HDCT-DI. The 5-year OS for HDCT-DI<70% was statistically inferior to HDCT-DI>70% OS. Complete response was developed in HDCT-DI<90% in 17 patients. 3 patients did not reach the ideal survival rate from the protocol.

Legal entity responsible for the study: Jung Woo Han
Funding: None
Disclosure: All authors have declared no conflicts of interest.

360P Primary central nervous system germ cell tumours: A single institution retrospective study
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Background: Germ Cell Tumors (GCTs) are 2% of intracranial neoplasms, mainly in the pineal/suprasellar region and in young ages. The overall prognosis, in tumors containing a non-gonadomatous component, is poor with a median 5 year overall survival (OS) of under 30%. Treatment recommendations suggest a multimodal approach.

Methods: We performed a retrospective review of all consecutive primary intracranial GCT patients diagnosed and treated at our institution from 1988 to 2015. Primary aim: to characterize the clinical, demographic and treatment data. Secondary aim: to evaluate overall survival (OS) at 5 and 10 years using the Kaplan-Meier method and related prognostic factors

Results: From a total of 45 cases, 30 were males, median age 11 years (P10-90: 5-27). The main symptoms were cephalalgia (45%), diabetes insipidus (31%) and vomiting (20%). 53% had endocrinologic disturbances, 44% visual field limitations and 20% pts Parinaud Syndrome. Sixty percent presented with intracranial hypertension. Primary location was the pineal and suprasellar in 56% and 28% of cases. Cranial and Neuroaxial Magnetic Resonance Imaging (MRI) was the preferred imaging method used in 91 and 53% pts, respectively. The diagnosis was reached by tumour markers in 22.2%, tumour biopsy in 26.6% and surgery in 51.1% pts. Tumour markers were elevated in 69% pts. Forty-nine percent of pts had pure germinoma, 15.5% pts had mixed germinoma and 35% pts non-germinoma. Sixty-nine percent of pts underwent intracranial decompression techniques. Sixty-nine percent of pts had chemotherapy regimens (PEI in 18 pts) and 82.2% pts had cranial radiotherapy (with simultaneous neuroaxial irradiation in 17 pts). Complete response was achieved in 91.1% of pts with 22.2% pts receiving surgery. The 5 and 10 OS rate was 88% and 85% respectively (98 and 80% for Germinoma and 82 and 75% for non-germinoma). OS values differences between histologies did not reach statistical significance. In the multivariate analysis only cranial radiotherapy and absence of recurrence were associated with improved survival (p = 0.003 and p = 0.016, respectively).

Conclusions: First line multimodality treatment achieves good clinical outcomes, with focus on cranial radiotherapy. Disease recurrence is associated with worse outcomes.

Legal entity responsible for the study: Instituto Portugues de Oncologia de Lisboa
Funding: None
Disclosure: All other authors have declared no conflicts of interest.
the brain was observed in 37 patients (82.2%). In 43 patients (95.6%) of 45 were also established metastases in other sites (extracranial lesions). Complete regression of metastases in extracranial lesions was achieved in 1 patient (2.3%), partial regression – in 26 (60.4%), stabilization in 13 (30.2%). The median time to disease progression was 5.5 months. The median survival of patients was 8.5 months.

Conclusions: The data presented indicate that the targeted therapy with BRAF inhibitors as monotherapy and also in combination with MEK inhibitors in patients with metastatic melanoma with brain metastases provides control over the disease in most patients and has a significant advantage with a group of historical control (chemotherapy = whole brain irradiation).

Legal entity responsible for the study: Russian N.N. Blokhin Cancer Research Center

Funding: Russian N.N. Blokhin Cancer Research Center

Disclosure: All authors have declared no conflicts of interest.

363P Radioprotective effect of xenon in radiation treatment for brain metastases

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Background: Surgical treatment, whole brain irradiation (WBI) and stereotactic radiation therapy (RT) are the main treatment strategies for solitary brain metastases. Applying additional boost to the bed of removed metastatic foci seems promising for enhancing local control, but increased radiation exposure affects the central regulation and processes that maintain homeostasis. The purpose of the study was to evaluate optimization of adjuvant RT with xenon due to its neurotrophic and neuroprotective effects.

Methods: 16 patients of the control group received WBI with additional boost once a day (60 Gy in 15 fractions), while 12 patients of the main group received similar RT plus inhalations of a xenon/oxygen mixture twice a week. Clinical and neurological examination was performed and the quality of life was assessed (using QLQ-C15 and BN-20 + 2 questionnaires) for all patients during the treatment. Adaptation reactions were identified and the ratio of their anti-stress/stress types (R as/s) was calculated for integral evaluation of the body condition, individual testing tension (Ut) at the Yin Tang point was studied and EEG parameters were analyzed.

Results: Only patients receiving xenon reported reduced rates of headaches and dizziness, disorders of higher nervous activity, reduced degrees of movement disorders; RT course for these patients was performed in compliance with the accompanying therapy. Assessment of the quality of life by the end of the treatment showed significant improvement in such criteria as physical health and loss of appetite, as well as pain relief, in contrast to the control group. Negative dynamics of integral body parameters, R as/s and Ut was lower than in the control group, and some EEG parameters were normalized after xenon therapy.

Conclusions: Xenon therapy is an effective optimization method for radiation treatment of patients with brain metastases. Its radioprotective and stress-limiting effects allow reduction of adverse effects and toxicity and improvement of the quality of life of patients.

Legal entity responsible for the study: Rostov Scientific Research Institute of Oncology, Russia

Funding: None

Disclosure: All authors have declared no conflicts of interest.
DEVELOPMENTAL THERAPEUTICS

Oncolytic herpesvirus therapy for mesothelioma: A phase I/IIa trial of intrapleural administration of HSV1716 (NCT01721018)

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Background: Malignant Pleural Mesothelioma (MPM) remains a major challenge with limited therapeutic options. Disease is frequently confined to the pleura, distant metastases are uncommon and intrapleural treatment is therefore appealing. HSV1716 is a 34-kDa oncolytic herpes simplex virus which, in pre-clinical studies, demonstrates cancer cell-specific HSV1716 infection and oncolysis and an anti-tumor immune response. We assessed the safety and potential for efficacy of intrapleural HSV1716 in patients with inoperable MPM.

Methods: We performed an open-label, dose escalation, phase I/IIa trial of intrapleural HSV1716. Patients with a histological diagnosis of MPM and indwelling pleural catheter (IPC) were eligible if they had performance status ≤ 2 and adequate hematologic, renal and liver function. Patients received 3x105 pfu HSV1716 through their IPC, 1–2 or 4 occasions a week apart, in 3 separate cohorts. The primary objective was to determine the safety and tolerability of intrapleur HSV1716. The secondary objectives were to assess HSV1716 replication and patient immune responses in pleural fluid and blood. An exploratory objective was to assess tumour response by CT, using modified RECIST criteria.

Results: Twelve patients were treated, 3 received 1 dose of intrapleural HSV1716, 3 received 2 doses and 6 received 4 doses. HSV1716 was well-tolerated with no HSV1716-related SAE and 17 HSV1716-related transient Grade 1-2 AEs. Evidence of HSV1716 replication (n = 9) and pleural T-cell cytokine responses (n = 8) were observed. Novel anti-tumor IgG responses were detected post treatment and their antigen targets identified by protein array. CT analysis on day 57 indicated 6 patients with stable and 6 patients with progressive disease. Median survival from treatment was 15 months for all patients and 18 months in patients with evidence of disease progression.

Conclusions: The study demonstrated an acceptable safety profile of intrapleural HSV1716 with evidence of viral replication and anti-tumour immunogenicity. This supports further studies in MPM, possibly involving combination with immune checkpoint inhibitors.

Clinical trial identification: NCT01721018

Legal entity responsible for the study: Virtu Biologics Ltd
Funding: Virtu Biologics Ltd

Disclosure: S. Danson: Advisory role for Incanthera Research funding from Lilly, GSK, Bristol-Myers Squibb, Idera, Incyte, Novartis, Boehringer. P. Wolf: Consulting/Advisory Role to Lilly, Theraxus. Research funding from AstraZeneca, Pfizer, Virtu. P. Fisher: Consulting/Advisory Role to Diagnostics. Research Funding from Pierre Fabre, Pfizer, Bristol-Myers Squibb. J. Ramadan, K. Simpson, R. Spear, K. Learmonth, J. Conner: Employee of Virtu Biologics. All other authors have declared no conflicts of interest.

Early FDG-PET response correlates with dose and clinical efficacy in patients with microsatellite stable (MSS) metastatic CRC (mCRC) treated with the CEA-CD3 T-cell bispecific antibody plus atezolizumab

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Background: CEA-CD3 TCB (RG7802, RO6958688) is a novel T-cell bispecific anti-CEA antibody designed to target CEA on tumor cells and CD3 on T cells. An ongoing phase Ib study (NCT02605715) is exploring the safety, tolerability and efficacy of CEA-CD3 TCB in mCRC patients. We report preliminary results of FDG-PET imaging as an early biomarker to predict the impact of CD3 point inhibitors.

Methods: In this study, CEA-CD3 TCB is given QW in combination with atezolizumab 1250 mg QW in patients with CEA-expressing solid tumors. As of March 3, 2017, a total of 35 MSS mCRC patients have been treated with CEA-CD3 TCB doses of 5-160 mg; 15 patients were evaluable for PET image analysis. On-treatment FDG-PET scans were performed at week 4 and compared with baseline. On-treatment changes in SUVmax, metabolic tumor volume (MTV) and total lesion glycolysis (TLG) were

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analyzed in up to 10 measurable lesions per patient, identified at baseline by an independent reviewer. The exploratory statistical analyses used semiparametric Gaussian regression models and Cox PH landmark analyses (for progression-free survival [PFS]).

**Results:** Early changes in FDG-PET parameters showed a dose–response relationship (MTV: $P = 0.0062$; TLG: $P = 0.0054$; SUV$_{max}$: $P = 0.0081$); notably all patients receiving doses $\geq 80$ mg/d (n = 7) showed decreases in SUV$_{max}$, TLG and MTV at week 4. Furthermore, week 4 reductions in FDG uptake (MTV: $P < 0.001$; TLG: $P = 0.034$; SUV$_{max}$: $P = 0.0061$) correlated with later tumor shrinkage (best change from baseline per RECIST v1.1). Reduction in MTV and TLG, but not SUV$_{max}$, correlated with decreases in soluble CEA levels measured at week 6 (MTV: $P = 0.013$; TLG: $P = 0.034$; SUV$_{max}$: $P = 0.54$) and longer PFS (MTV: $P = 0.013$; TLG: $P = 0.052$; SUV$_{max}$: $P = 0.85$).

**Conclusions:** In MSS mCRC patients, changes in MTV, TLG and SUV$_{max}$ correlated with dose and tumor shrinkage. Decreases in 2 FDG parameters (MTV and TLG) correlated with a reduction in soluble CEA levels. Early on-treatment changes in FDG-PET can serve as a pharmacodynamic biomarker related to treatment efficacy.

**Clinical trial identification:** NCT02607013

Legal entity responsible for the study: F. Hoffmann-La Roche Ltd.

**Funding:**

- **Legal entity responsible for the study:**
  - **Disclosure:**
  - **Authors:**
  - **Conflict of interest:**

**Disclosure:**

- **Authors:**
- **Conflict of interest:**

**Background:** Poly(ADP-ribose) polymerase inhibitors (PARPis) represent a class of antitumor agents that exert their cytotoxic effects by inhibiting PARP activity. Some PARPis are capable of trapping PARP proteins on DNA further augmenting cell death. Poly (ADP-ribose) polymerase inhibitors (PARPis) are capable of trapping PARP proteins on DNA further augmenting cell death. Furthermore, PARP inhibition has been shown to enhance the antitumor activity of several chemotherapy regimens.

**Methods:** This two-phased study (NCT02361723) consists of a Phase 1a dose-escalation/dose-finding component to establish the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of BGB-290 in patients with solid tumors and a two-part Phase 2 component that includes expansion in targeted indications (Part A) and the effect of food on the BGB-290 pharmacokinetic (PK) profile (Part B).

**Results:** As of 1 May 2017, Phase 1A had completed enrollment (n = 45); 3 patients remain on treatment. Objective responses were observed across the dose range (2–90 mg/d). Of the 23 evaluable patients with gynecological cancer, 10 (43%) achieved an objective response per RECIST 1.1 (n = 3; complete; n = 7; partial). More patients with germline BRCA1/2-mutated ovarian cancer achieved an objective response (n = 7/12, 58%) than patients not carrying the mutation (n = 2/8, 25%). Drug-related adverse events (AEs) reported in $\geq 10\%$ of patients were nausea, fatigue, anemia, vomiting, diarrhea, anorexia, and neutropenia. Anemia and neutropenia were the most common drug-related Grade 3 AEs; no Grade 4 drug-related AEs were reported. Three BGB-290-related serious AEs were reported (anemia, n = 2; nausea, n = 1). Four deaths were associated with an AE; however, none were considered drug-related. The BGB-290 RP2D was determined as 60 mg BID and is being evaluated in Phase 2 to determine antitumor activity and food effects. Dose escalation to determine MTD with QD dosing is ongoing.

**Conclusions:** BGB-290 has demonstrated a favorable safety profile and promising preliminary antitumor activity in phase 1A; phase 2 is ongoing evaluating in patients with ovarian, breast, prostate, gastric and small cell lung cancer.

**Clinical trial identification:** NCT02631723

Legal entity responsible for the study: Beigene Ltd.

**Funding:** Beigene Ltd.

**Disclosure:**

- **Authors:**
- **Conflict of interest:**

**Background:** Aberrant PI3K/Akt/mTOR (PAM) pathway signaling is observed in various tumors and confers resistance to standard therapies. M2698 is an oral, brain penetrant, potent and selective p70S6K/Akt/1/3 inhibitor that can block signaling from Akt feedback loop activation, a possible tumor escape mechanism.

**Methods:** Patients (pts) with advanced cancer were given oral M2698 daily (PO 15–380 mg) in 21-day (d) cycles in a 3 + 3 dose escalation (DE) design. Response was assessed every 2 cycles. An expansion phase in pts with PAM pathway tumor alterations is ongoing.

**Results:** Overall, 50 pts received M2698 monotherapy (DE, n = 40; expansion, n = 10); DE data presented only (cut-off 10/27/16). Treated pts had a median age of 56 years (14 men, 26 women). Tumor types included breast (n = 7), colon (n = 4), lung (n = 4) and other (n = 23). In the DE phase, 35/40 pts were evaluable. Two pts had a dose limiting toxicity (DLT; 60mg and 160mg) and drug-related Grade $\geq$3 adverse events (AEs) occurred in 6/40 (15%) of pts. AEs leading to dose reductions occurred in 1 pt at $<320$ mg/d and in 3 pts $\geq320$ mg/d. Of the 32 DE pts (without DLT) who completed treatment by the data cut-off, 6 pts (19%) remained on treatment (Rx) for $\geq180$ days (min, max range 21 to 504 days) [Table]. Exposure of M2698 increased dose proportionally and $86\%$ phospho-S6 inhibition in tumor was achieved in 27 paired biopsies from pts treated with doses $\geq110$ mg/d. Expansion phase dose was 240 mg/d. Tissue molecular analysis and liquid biopsies were performed. Analysis is ongoing.

**Table:**

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<tr>
<th>Dose level mg/d</th>
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**Conclusions:** M2698 was well tolerated and provided stable disease over a wide range of doses.

**Clinical trial identification:** NCT01971515

Legal entity responsible for the study: Merck KGaA, Darmstadt, Germany

**Funding:** Merck KGaA, Darmstadt, Germany

**Disclosure:** G. Lopes, R. Kurzrock. Research funding from Merck. A. Victor. Merck employee. J. Shaw, R. Kaela: EMD Serono employee. All other authors have declared no conflicts of interest.
A Phase 1 PK/PD Study of ASN003, a novel highly selective BRAF and PI3K inhibitor, in patients with advanced solid tumors

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Background: Dysregulation of the FGF/FGFR signaling pathway has been associated with many developmental disorders and variations of cancers. TAS-120 is an oral, highly selective covalent FGFR inhibitor with potent antitumor activity in vitro and in vivo models with FGFR pathway aberrations.

Methods: This FIH study consists of dose escalation phase (DE) and expansion phase (EX). The objectives of this study are to determine the maximum tolerated dose (MTD)/recommended dose (RD) and to investigate the safety, pharmacokinetics, pharmacodynamics, and efficacy. In DE, the first three cohorts were evaluated by a single patient then a 3+3 design is used which is currently ongoing. Pts with FGFR abnormalities can be enrolled to EX during the evaluation of DE with dose lower than maximum administered dose under evaluation. TAS-120 was administered orally three times weekly (Monday-Wednesday-Friday) in a 21-day cycle.

Results: As of 3 Apr 2017, 36 pts (34% FGFR with genetic abnormalities) were enrolled (DE: 26 pts, EX: 10 pts). Tumor types enrolled were bladder cancer (n = 8), colorectal cancer (n = 7), kidney cancer (n = 4), gastric, esophageal and pancreas cancer (n = 3 each), and others (n = 8). Pts were treated in 8 dose cohorts of 8 - 160 mg. MTD has not been reached. The most common drug-related AEs (all AEs >10%) were hyperphosphatemia (12%), anemia (12%), and diarrhea (10%). Grade >3 adverse events were hyperphosphatemia and anemia (12%). Grade >3 hyperphosphatemia has not been observed. Hyperphosphatemia was managed with dose interruption or reduction in addition of phosphate binders. Drug-related SAE has not occurred. TAS-120 exposure increased with dosage. Mean Cmax and AUC0-24 at 160 mg were 1,192 ng/mL and 9,972 ng*h/mL, respectively, with a mean T1/2 of 2.67 hrs and apparent T1/2 of 6.68 hrs. Two pts showed the clinical response, one of them was gastric cancer with FGFR2 amplification at 80 mg, and the other was esophageal cancer (FGFR status is under evaluation) at 120 mg. Moreover, two biliary tract cancer with FGFR2 fusion at 60 mg, and one bladder cancer at 36 mg (FGFR status is unknown) had stable disease > 24 weeks.

Conclusions: TAS-120 was well-tolerated, and the safety profile was confirmed up to 120 mg. The ongoing DE and EX are still under evaluation and RD will be determined.

Clinical trial identification: Clinical trial information: JapicCTI-142552
Legal entity responsible for the study: Eisai Inc.
Funding: Eisai Inc.

Legal entity responsible for the study: Eisai Inc.
Funding: Eisai Inc.

Phase 1 Study of E7046, a PG2 Receptor EP-4 inhibitor that targets immunosuppressive myeloid cells in the tumor microenvironment

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Background: E7046 is a selective small molecule antagonist of the prostaglandin E2 receptor type-4 that inhibits the differentiation of mononuclear myeloid lineage cells towards a pro-tumorigenic phenotype in the TME. This is a first-in-human study of single-agent E7046.

Methods: Key eligibility criteria: patients (pts) ≥18 years with selected advanced cancers with high levels of myeloid infiltrate. The dose-escalation phase consisted of 6-pt cohorts of 125, 250, 500, and 750 mg (once-daily, oral, 21-day cycle) doses of E7046. Primary objectives were safety/tolerability, maximum tolerated dose (MTD) and/or RD. Secondary objectives included PK and initial anti-tumor activity; exploratory objectives included PD assessment on immune cells in tumor infiltrate and in peripheral blood and metabolic response by 18F-FDG-PET. Results: 30 pts received E7046 (median age 58 yrs [24-78], 22% of whom were male). Most common tumor types were colorectal cancer (20%) pancreatic cancer (29%) and SCCCHN (13%). No DLTs were observed and the MTD was not reached. The most frequent drug-related adverse events (AEs) were diarrhea (20%), decreased appetite, fatigue and nausea (13% each). Drug-related AEs of Gr 3/4 occurred in 4 pts (diarrhoea, anaphylactic reaction, hyperuricemia, rash, generalized rash). 2 pts had drug-related serious AEs (rash, allergic reaction, fever in 1 pt; hyperuricemia, acute renal failure [Gr 2] in 1 pt). 3 pts discontinued treatment due to AEs (bowed osteoblast, allergic reaction, abdominal pain). There were no drug-related deaths. E7046 exposure was dose proportional up to 500 mg with no incremental increase in exposure at 750 mg. E7046 was extensively metabolized; elimination half life was ~12hr and accumulation on multiple dosing was ~2-fold. 2 pts are ongoing and preliminary efficacy showed no major responses, 4 pts with durable SD or clinically stable (>4 mos) and 4 pts with 18F-FDG-PET metabolic responses.

Conclusions: Single-agent E7046 was tolerated with no MTD reached in heavily pre-treated pts with myeloid-rich tumors. PD analysis of immune cell modulation helps determine the RPD will be presented at the meeting.

Clinical trial identification: Clinical trial information: NCT02540291
Legal entity responsible for the study: Eisai Inc.
Funding: Eisai Inc.
A highly-selective oral small-molecule Chk1 inhibitor that results in tumor shrinkage and growth delay in xenograft models.

**Methods:** This Phase I trial enrolled pts with refractory solid tumors and ECOG 0-1 status. Patients received IV gem 1000 mg/m² followed ~24 hours later by GDC-0575 (15-60 mg) PO, or IV gem 500 mg/m² followed ~24 hours later by GDC-0575 (45-105 mg) PO, weekly for 2-3 of 4-week cycles. TP53 was evaluated in archival tumor tissue by gene sequencing. Safety, pharmacokinetics (PK), pharmacodynamics, and tumor response by RECIST v1.1 were investigated.

**Results:** Of 81 pts treated, 73% were female, the median age was 56 years (range 27-75), and 48% were ECOG PS 0. The most common tumor types were breast (46%), and soft tissue sarcoma and NSCLC (both 7%). Dose escalation was halted at GDC-0575 60 mg PO, or IV gem 500 mg/m² followed ~24 hours later by GDC-0575 (45-105 mg) PO, weekly for 2-3 of 3-week cycles. TP53 was evaluated in archival tumor tissue by gene sequencing. Safety, pharmacokinetics (PK), pharmacodynamics, and tumor response by RECIST v1.1 were investigated.

**Conclusions:** The Chk1 inhibitor GDC-0575 can be safely combined with a standard or modified dose and schedule of gem. Hematological toxicities were frequent but manageable. Preliminary anti-tumor activity was observed in patients with a variety of refractory solid tumors treated with GDC-0575 in combination with gem 500 mg/m².

**Clinical trial identification:** NCT02164251

Legal entity responsible for the study: Genentech, Inc.

Funding: Genentech, Inc.

Antibody–drug conjugates combine the specific targeting and antitumor activity of monoclonal antibodies with the potent cell killing activity of cytotoxic small molecule drugs. IMAB362 is a monoclonal antibody specific for the tight junction protein Claudin 18.2 (CLDN18.2). In normal tissue, CLDN18.2 is exclusively expressed in the gastric mucosa. In the context of malignant transformation, CLDN18.2 can be found in gastric tumors as well as tumors from organs that do not normally express CLDN18.2 (e.g., pancreas). Preclinical characterization of IMAB362 conjugated to the antitumor molecule, monomethyl auristatin E, with a valine–citrulline linker (IMAB362–vcMMAE) is presented here.

Methods: IMAB362–vcMMAE binding characteristics and internalization were assessed in CLDN18.2-expressing human cell lines. Cell viability and IMAB362–vcMMAE-mediated cytotoxic effects (direct and indirect [bystander]) were also assessed in CLDN18.2 in vitro models. Xenograft mouse models of pancreatic and gastric cancers were developed to assess the cytotoxic and antitumor effects of IMAB362–vcMMAE in vivo.

Results: IMAB362–vcMMAE showed a slightly decreased relative binding affinity on CLDN18.2-transfected cells and cells that endogenously express CLDN18.2 compared with unconjugated IMAB362. In cell lines that internalized IMAB362–vcMMAE, cell viability was reduced by 45–90%. EC50 (cell viability < 30 ng/mL). By contrast, no reduction in cell viability occurred in cells without target expression. IMAB362–vcMMAE produced CLDN18.2-negative cell death via bystander effect in vitro (so-called tumor cells). In vivo, intravenous IMAB362–vcMMAE resulted in dose-dependent inhibition of tumor growth as well as prolonged survival in early and advanced tumors in both pancreatic and gastric cancer mouse models. Significant antitumor activity was observed after a single 8 or 16 mg/kg IV bolus injection. No systemic or organ-specific IMAB362–vcMMAE-related toxicity was observed in the mice.

Conclusions: IMAB362–vcMMAE is a highly specific and potent antibody–drug conjugate against in vivo and in vitro models of gastric and pancreatic cancers.

Legal entity responsible for the study: Ganymed Pharmaceuticals AG, A company of Astellas Pharma, Inc.

Funding: Ganymed Pharmaceuticals AG, a company of Astellas Pharma, Inc. Disclosure: R. Mitnacht-Kraus: Employee of Ganymed Pharmaceuticals AG, a company of Astellas Pharma, Inc. In addition, Dr. Mitnacht-Kraus has a patent P-24PCT issued. U. Sahin: Patent owner, ex-shareholder and cofounder of Ganymed Pharmaceuticals AG and Founder/CEO/shareholder of BioNTech Holding outside the submitted work. Dr. Sahin has several patents issued to this work that have been acquired by Astellas.

A novel mri-based patient selection strategy identifies fibroblast growth factor receptor (FGFR) inhibitor-sensitive tumors: Results from rogaratinib Phase 1 study

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Background: Altered FGFR signaling is a potential target for anticancer therapy. Rogaratinib (BAY1163877) is an oral inhibitor of FGFRs 1-4. Screening for patients based on tumor FGFR1-3 mRNA overexpression, we reported in a phase I study that selected urothelial carcinoma patients were highly sensitive to rogaratinib treatment (Neijssel1978741, Joergel et al, ESMO 2016). Here we further identify patients sensitive to rogaratinib with malignancies not previously identified as being driven by FGFRs.

Methods: Subjects with treatment-refractory advanced or metastatic solid tumors were screened for high FGFR1-3 mRNA expression levels by RNA in situ hybridization (RNAscope®), Advanced Cell Diagnostics, Inc., Newark, CA and NanoString® assay. Nanosting Technologies, Inc., Seattle, WA) from fresh or archival tumor specimens. FGFR-positive patients were treated with #800 mg BID on a continuous 21-day cycle. Responses were assessed by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Results: More than 500 patient biopsies were screened for FGFR1-3 mRNA levels. Seventy-two FGFR-positive patients were treated with rogaratinib, with 63 evaluable for response. Clinical responses were observed in tumor types not previously associated with FGFR alterations, including a partial remission (PR) in a patient with a FGFR1 mRNA-positive adenoid cystic carcinoma of the tongue and a PR in a FGFR3 mRNA-
positive head and neck squamous cell carcinoma patient. Long-lasting stable disease with tumor shrinkage was also seen in patients with a) FGFR3 mRNA-positive gastric cancer, b) FGFR1 mRNA-positive lung squamous cell carcinoma c) FGFR1 mRNA-positive lung adenocarcinoma, d) FGFR2 mRNA-positive breast cancer and e) FGFR1 mRNAl-positive hemanioendothelioma with complete disappearance of edema over 18 months.

Conclusions: Patient selection for treatment with regorafenib based on quantification of FGFR1-3 mRNA isoforms in all tumor types irrespective of underlying data on DNA alterations is feasible and yields clinically meaningful responses in tumor types not been previously associated with altered FGFR signaling.

Clinical trial identification: NCT01976741

Legal entity responsible for the study: Bayer AG

Disclosure: S. Bender, P. Ellingshaus, M. Ocker: Employment: Bayer AG. S. Ince, P. Rajagopalan: Employment: Bayer HealthCare Pharmaceuticals. All other authors have declared no conflicts of interest.

A phase 1b study evaluating the safety and pharmacokinetics (PK) of regorafenib (REG) in combination with cetuximab (CTX) in patients with advanced solid tumors

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Background: Combining REG with CTX may overcome intrinsic and acquired resistance in EGFR-sensitive and -resistant tumors. We evaluated the safety, PK, maximum tolerated dose (MTD), and preliminary efficacy of REG plus standard dose of CTX (initial 400 mg/m2 intravenously followed by 250 mg/m2 weekly) in a phase 1b study. Final results from the intermittent REG dosing arm (3 weeks on/1 week off) are reported, with final results from the terminated continuous REG dosing arm (n = 11) previously presented (Weekes et al. ACR 2016 abstract CT148).

Methods: This was an open-label, dose-escalation (3 + 3 design) study in patients with locally advanced or metastatic solid tumors who progressed after standard therapy. The starting dose of REG was 120 mg once daily (QD) in a 28-day cycle (3 weeks on/1 week off) plus CTX. If tolerable, REG was escalated to 160 mg QD. If not tolerable, the REG dose was reduced to 80 mg QD. Dose-limiting toxicities (DLTs) were evaluated in Cycle 1. Adverse events (AEs) were graded according to NCI-CTCAE v4.03. Antitumor activity was assessed using RECIST v1.1.

Results: As of January 31, 2017, 31 patients received REG in an intermittent schedule plus CTX. 8 patients received REG 120 mg and 23 received REG 160 mg. One DLT of grade 3 hand–foot skin reaction was reported in 6 evaluable patients at the 120 mg dose level. No DLT was confirmed at the 160 mg dose level. The MTD was declared at the standard dose of REG 160 mg QD (3 weeks on/1 week off) plus the standard dose of CTX. The most common AEs, regardless of relationship to study drug, were hypophosphatemia (42%), fatigue (39%), and nausea (39%). The most common grade ≥3 REG-related AEs were hypophosphatemia (23%) and fatigue (10%). REG AUC0–24h was 29.1 mg·h/L at 160 mg and 17.4 mg·h/L at 120 mg. CTX had no effect on the PK of REG. One patient (120 mg REG) had a partial response; 6 (160 mg REG), 29% and 2 (120 mg REG), 23% patients had stable disease.

Conclusions: REG at 160 mg QD (3 weeks on/1 week off) plus standard dose of CTX was tolerated with no unexpected toxicities. Observed AEs were in line with known REG and CTX safety profiles.

Clinical trial identification: NCT01976368

Legal entity responsible for the study: Bayer

Conclusions: Hence, current work is conducted to analyze by gene array profiling the differences in NRPI and other cancer promoting receptors between responder and non-responder populations. This is a prerequisite to decide whether MTP-NRPI could be developed in this indication, particularly by associating it to another drug in the non-responding population.

Legal entity responsible for the study: INSERM U109, "Microenvironmental Niche in Tumorigenesis and Targeted Therapy" MN17 lab, Labex Medalis, University of Strasbourg, France.

Funding: Labex Medalis, University of Strasbourg, France.

Disclosure: All authors have declared no conflicts of interest.

A phase I dose-escalation study of the novel peptide ALM201 in patients (pts) with advanced solid tumours

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Background: ALM201 is a novel 23-amino acid peptide derived from FKPB-L, a human endogenous protein with inherent anti-angiogenic activity. Pre-clinically, ALM201 inhibits cell migration, invasion and neo-vascular formation without effects on cell cycle or proliferation.

Methods: We enrolled pts with solid tumours using a single patient (10-40mg) then 3+3 (80-300mg) dose escalation design. ALM201 was administered subcutaneously (S.C.) once daily on days 1-5, 8-12, and 15-19 every 21 days. All pts continued until disease progression (PD) or dose-limiting toxicity (DLT). Primary objectives were to determine tolerability and recommended phase II dose (RP2D) of ALM201. Secondary objectives were to determine the pharmacokinetics (PK) and anti-tumour activity. Plasma and urine samples were analysed by a validated LC-MS/MS method.

Results: We report interim data in 18 evaluable pts enrolled in 8 dose levels. Cancers included ovarian (5), colorectal (4), NSCLC (2), endometrial (1), gallbladder (1), cervical (1), urothelial (1), renal (1), pancreatic (1) and mesothelioma (1). Doses of 10-300mg were well tolerated. No DLTs were observed. The only toxicity grade 1 injection site skin reaction. Median treatment duration was 11.1 weeks (range 3-18 weeks).

Two patients had stable disease for up to 6 cycles prior to progression. Maximal plasma concentrations were consistently seen up to 6h above 40mg. Plasma concentrations were consistently seen up to 6h above 40mg. Plasma and urine samples were analysed by a validated LC-MS/MS method.

Conclusions: Monotherapy ALM201 administered S.C. demonstrated a very good activity. Plasma and urine samples were analysed by a validated LC-MS/MS method.

Disclosure: R. Kennedy: Employee at Almac Diagnostics & Almac Group. A. Cranston: Holder of an IP in RNA Guardian. Travel grant from Nucana. All other authors have declared no conflicts of interest.

Efficacy of pembrolizumab in phase 2 KEYNOTE-164 and KEYNOTE-158 studies of microsatellite instability high cancers


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Background: A high level of microsatellite instability (MSI-H) is indicative of a tumour deficient in mismatch repair (dMMR). This and lack of toxic metabolite accumulation indicate NUC-3373 has a favorable PK profile compared to the established fluoropyrimidines.

Clinical trial identification: ClinicalTrials.gov NCT02723240 EudraCT Number: 2015-002250-13 Release date: December 8, 2015

Legal entity responsible for the study: University of Oxford

Funding: Nucana BioMed Ltd

Disclosure: D. Harrison: Advisory in Cytoysystems, Nucana and Ryboquin. Leadership role in Ryboquin. The institute received research funding from Nucana Ltd and Ryboquin Ltd. T.R.J. Evans: Advisor role up to 4th month Support Influence, GSK, Baxter and Celgene. The institute received research funding from several Pharmaceutical companies. S.P. Blagden: Advisory role in Celgene and Novartis. Holder of an IP in RNA Guardian. Travel grant from Nucana. All other authors have declared no conflicts of interest.
Methods: KN164 enrolled pts with MSI-H colorectal cancer (CRC) and ≥2 prior thera-
pies, whereas the multicohort KN158 study included pts with MSI-H non-CRC and ≥1 prior therapy. MSI-H status was determined locally by IHC or PCR or centrally by PCR. Eligible pts in both studies received pembrolizumab 200 mg QW. Tumor re-
response was assessed every 9 wk. Primary endpoint was ORR by independent central re-
view per RECIST v1.1. Database cut-off date was Feb 17, 2016 for KN164 (≥54 wk follow-up) and Jan 27, 2017 for KN158 (≥27 wk follow-up).

Results: KN164 enrolled 51 pts with MSI-H CRC (90% with ≥2 prior therapies) and KN158 enrolled 75 pts with MSI-H non-CRC (52% with ≥2 prior therapies), at data cut-off. Tumor types represented in KN158 in at least 2 pts included endometrial (n = 14), gastric (n = 11), small intestinal (n = 10), pancreatic (n = 9), biliary (n = 8), mesotheloma and small cell lung (n = 3 each), adenocarcinoma, thyroid, and bladder (n = 2 each). ORR was 27.9% (n = 17 [all confirmed]; 95% CI 17.1%-40.8%) for MSI-H CRC, and 37.6% (n = 29 [23 confirmed and 6 unconfirmed]; 95% CI 26.9%-49.4%) for MSI-H non-CRC. Median DOR was not reached for MSI-H CRC (range 2.9-11.3+ months) or MSI-H non-CRC (range 2.4-9.2+ months). Median OS was not reached for either MSI-H CRC or MSI-H non-CRC, with 6-mo OS rates of 87% and 73%, respectively.

6-mo PFS rates were 43% for MSI-H CRC and 45% for MSI-H non-CRC. (47%) pts with MSI-H CRC and (79%) with MSI-H non-CRC had serious drug-related AEs. The safety profile was consistent with that previously seen for pembrolizumab.

Conclusions: Pembrolizumab provides robust antitumor activity with durable re-
sponses in heavily pretreated pts with MSI-H cancers.


Legal entity responsible for the study: Merck & Co., Inc.

Funding: Merck & Co., Inc.

Disclosure: L. Diaz: Travel expenses from Merck & Co., Inc. A. Matalaba: Advisory board for Merck Serono, Ebeidomics, Kyowa Kirin Pharma, Bayer, Novartis, Bristol-Myers Squibb, Symphogen, Gennab, Amgen, Biothera, Nektar, GSK, Oncovir, Pfizer, Seattle Genetics, Plexus Bio, Roche-Genentech. Speakers’ bureau for MSD T. W. Kim: Advisory board for Merck. R. Geva: RG: Advisory board member for Bayer, MSD & Novartis. Honoraria from Bristol-Myers Squibb, Lilly, Medison, Roche, Novartis and Jansen. E. Van Cutsem: Employment and funding from Amgen, Boehringer, Celgene, Ipsen, MSD, Merckserono, Novartis, Roche, Sanofi and Servier. T. Andre`: Honoraria from Boehringer Ingenheim, Merck, Serono, Baxter, Bayer and Roche. P.A. Asciento: Advisory board member for Bristol Myers-Squibb, Roche-Genentech, MSD, Novartis, Array, Amgen, Merck Serono, and Pierre Fabre. M. Maio: Honoraria, travel expenses and consulting fees from Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, GSK, & MedImmune. R. Guimbaud: Advisory board member for Bayer. Travel expenses, including accommodations from Roche, Ipsen, Lilly and Sanofi, D. Jaeger: Consulting or advisory roles and Roche, Bristol-Myers Squibb & Bayer. T. Yoshino, A. Joe, B. Lam, J. Ding, S. Pruitt, S.P. Kang: SPK is employed by Merck & Co., Inc. and may own stock or equity in the company. T.T. Le: Research grants and honoraria from Merck & Co., Inc. All other authors have declared no conflicts of interest.

38BP Preliminary results from a subset of patients (pts) with advanced head and neck squamous carcinoma (HNSCC) in a dose-escalation and dose-expansion study of BGB-A317, an anti-PD-1 monoclonal antibody (mAb)

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Methods: This ongoing, open-label, dose-escalation/expansion study is being conducted to evaluate the safety, tolerability and anti-tumor activity of BGB-A317 in pts with advanced solid tumors. Pts with histologically confirmed advanced GC or EC were eligible and treated with BGB-A317 at 2 mg/kg or 5 mg/kg every two weeks (Q2W) or QW. Adverse events (AEs) were assessed per NCI-CTCAE v4.0. Tumor assessments were performed approximately every two weeks via RECIST v1.1. Results: As of 6 MAR 2017, 73 pts (median age 62 yrs (22-81)) with recurrent/refractory GC (n = 28) or EC (n = 27) were treated. Most were Caucasian (n = 36) and all pts had received ≥1 prior line of anti-cancer treatment. Median treatment duration was 51 days (5-363); 19 pts remain on study. The most common treatment-emergent AEs were fatigue (n = 11), nausea (n = 9) and dysphagia (n = 8); 46% pts experienced AEs ≥Grade (Gr) 3 but none were treatment related. One serious AE (diabetes (Gr 2)) was considered related to treatment by investigators. Of the 47 evaluable pts, the disease control rate, defined as the proportion of pts who achieved complete or partial response (CR or PR) or stable disease (SD), is 32%. Pts have been reported in 3 pts (GC = 2; EC = 1) with duration of responses being 96, 125 and 188 days respectively, 2 pts are still on treatment; 5 initial documentations of PRs awaiting confirmation (GC, n = 2; EC, n = 3) have been reported in 12 pts with SD (GC = 5; EC = 7).

Conclusions: BGB-A317 appears to be generally well tolerated in pts with recurrent/refractory GC or EC. The preliminary safety profile and anti-tumor activity appear to be consistent with other checkpoint inhibitors and support continued exploration and de-
velopment of BGB-A317 in pts with advanced GC or EC.

Clinical trial identification: NCT02407990, March 26, 2015

Legal entity responsible for the study: Beigene Ltd.

Funding: Beigene Ltd.

Disclosure: J. Desai: Honoraria: Bayer, Merck Serono, Novartis. Consulting or advis-
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387P Preliminary results from subsets of patients (pts) with advanced gastric cancer (GC) and esophageal carcinoma (EC) in a dose-escalation/ expansion study of BGB-A317, an anti-PD-1 monoclonal antibody (mAb)

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Preliminary results from a subset of patients (pts) with advanced ovarian cancer (OC) in a dose-escalation/expansion study of BGB-A317, an anti-PD-1 monoclonal antibody (mAb)

Methods: An open-label, multi-center, dose-escalation/expansion study is being conducted to evaluate the safety, tolerability and anti-tumor activity of BGB-A317 in pts with advanced solid tumors. Pts with histologically confirmed advanced OC were eligible to receive pre- или mediated binding to macrophages/myeloid-derived suppressor cells (MDSCs). The suppression of PD-1/PD-L1 and the predominance of macrophages and MDSCs have been reported in OC supporting the rationale of evaluating BGB-A317 in OC pts with PD-L1 binding to PD-1 restoring T-cell-mediated tumor inhibition. The Fc-hinge region has been engineered to preclude FcRn mediated binding to macrophages/myeloid-derived suppressor cells (MDSCs).

Background: BGB-A317 is a humanized IgG4 anti-PD-1 mAb that blocks PD-L1/2 binding to PD-1 restoring T-cell-mediated tumor inhibition. The Fc-hinge region has been engineered to preclude FcRn mediated binding to macrophages/myeloid-derived suppressor cells (MDSCs). The suppression of PD-1/PD-L1 and the predominance of macrophages and MDSCs have been reported in OC supporting the rationale of evaluating BGB-A317 in OC pts with PD-L1 binding to PD-1 restoring T-cell-mediated tumor inhibition. The Fc-hinge region has been engineered to preclude FcRn mediated binding to macrophages/myeloid-derived suppressor cells (MDSCs).

Results: As of 6 Mar 2017, 51 pts [median age 62 (19–80) yrs] with recurrent/refractory OC were enrolled. Most pts were Caucasian (88%), all had received ≥1 prior line of anti-cancer treatment (median 3 [1–12]). Median duration of treatment was 88 (22–446) days, 7 pts remain on study. The most common treatment-emergent AEs were nausea (37%), fatigue (28%), and abdominal pain (28%). 49% of pts experienced an AE ≥ Grade 3 (11%); diarrhea (n = 1) and nausea (n = 1) were Gr 3 AEs considered treatment-related by investigators. Musculoskeletal pain, pyrexia, and colitis were serious AEs considered treatment-related by investigators (n = 1, each). Among 51 evaluable pts, the disease control rate is 43%; 2 PRs have been reported including 1 pt who remains on study and to date has achieved an 89% reduction in target lesions.

Conclusions: BGB-A317 appears to be generally well tolerated in pts with recurrent/refractory OC. The preliminary safety profile and anti-tumor activity support continued investigation of BGB-A317 in this setting.

Clinical trial identification: NCT02407990, March 26, 2015
Patients had biopsies at baseline and after 28 days of treatment for planned correlative testing. **Results:** To date, 38 patients (pts) have been enrolled. Median number of prior ther- apies was 4 (1-8). Only 7 (18%) of 5 ovarian, 2 breast pts had known germline BRCA mu- tation. The first two pts on DL (I 300mg: A 400mg) experienced DLTs of diarrhea and vomiting. Therefore, 6 pts were treated on DL-1 (O 300mg: A 320mg). There were no DLTs on DL-1, therefore, 6 additional pts were treated on DL1. There were no DLTs on re-explored DL1. Continuous PAR inhibition (Cmin,ss) in seven Phase I–III clinical studies. **Conclusions:** Continuous PAR inhibition (Cmin,ss) in seven Phase I–III clinical studies.

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**393P** Pharmacodynamic (PD) biomarkers for the p70S6K/Akt inhibitor, M2698: Translation from animal to human and relevance to dose selection

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**Background:** M2698 is an oral, potent and selective inhibitor of p70S6K/Akt1/3 in the PAM pathway with the potential to block signaling from the Akt feedback loop and overcome tumor resistance. Preclinical studies suggest a steep exposure–adverse event relationship. Therefore, insights into drug-dependent target modulation (56 phosphor- ylation (pS6) inhibition) and its association with efficacy could inform dose selection.

**Methods:** Pharmacokinetic (PK) data from the phase I, first-in-human (FFH) dose escalation trial conducted in patients with advanced cancer who received daily (d) oral M2698 (15–320mg/d) were evaluated by nonlinear, mixed effect modeling. Using a PK/ PD model developed with data from a breast tumor cell line derived xenograft (CLDX) in mice, tumor pS6 time profiles in humans were simulated using a mouse PD model driven by human PK. Model predictions were calibrated by comparing simulations to clinical observations, with an assumed variation in sensitivity (R²) to pS6 between CLDX and human tumors. Predicted pS6 time profiles and clinically observed pS6 in- hibition in human tumors and peripheral blood mononuclear cells (PBMC) informed the dose escalation decision in the FFH study.

**Results:** M2698 PK profiles were best described by a two-compartment linear model with transit compartments for delayed absorption. Consistent exposure-dependent ef- fects of pS6 inhibition in PBMCs were observed at 160–320 mg/d, with 70–80% pS6 in- hibition observed in some tumors. Based on predicted pS6 inhibition, CLDX tumors were 2-3x more sensitive than human tumors. Applying a 2-3x higher IC50 simulations suggested that 250–350mg/d would achieve the PD threshold of continuous tumor pS6 inhibition > 80% in 90% of a human population, leading to escalation to 380mg/d.

**Conclusions:** Understanding inter-species variation can improve the precision of preclinical-to-clinical translation. For M2698, preliminary clinical PD data showed that human tumors were 2-3x less sensitive to pS6 inhibition than CLDX tumors in mice. Collective PBMC and tumor PD outcomes suggest that 160-320 mg/d M2698 may result in considerable pS6 inhibition, a range for selection of a phase 2 dose.

**Clinical trial identification:** NCT01971515

**Legal entity responsible for the study:** Merck KGaA

**Funding:** Merck KGaA


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**394P** Phase 1 study of ipatasertib (AKT inhibitor) for investigating safety, tolerability, pharmacokinetics (PK), efficacy, and biomarkers in Japanese patients (pts) with solid tumors including castration-resistant prostate cancer (CRPC)

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**Background:** Ipatasertib is a highly selective small-molecule inhibitor of AKT showing antitumor activity. Clinical efficacy and safety in non-Japanese pts with metastatic prostate cancer (CRPC)

**Conclusions:** Discrepancy between biologically and clinically effective olaparib doses is explained by a need for continuous >95% PAR inhibition. Both the 400 mg bd capsule and 300 mg bd tablet dose, used in the ongoing clinical programme, provide this. Dosing schedule data suggest continuous PAR inhibition is also needed for long-term responses. These data highlight an important principle for treatment of patients with PARP inhibitor monotherapy.

**Legal entity responsible for the study:** AstraZeneca

**Funding:** AstraZeneca


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**392P** Generation of a novel preclinical PK/PD model provides insights into PARP inhibitor clinical monotherapy activity

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**Background:** In Phase II trials, an olaparib capsule dose that inhibits PARP (100 mg bd) was clinically inferior to the MTD (400 mg bd). Using an in vivo model, we investigated this discrepancy and the effect of dose and schedule on tumour progression. **Methods:** PK, PD and antitumour activity were assessed using olaparib (100, 50, 25, 10, 5 mg/kg/d) in a breast cancer patient-derived xenograft (PDX) with mutated BRCA2 and TP53. We studied the relationship between PARP1 inhibition and DNA single-strand breaks (SSBs) by creating a mathematical model. We also compared PK/PD and PD model parameters with free platinumalabirap steady-state plasma concentration (Css,ss) in seven Phase I–II clinical studies. **Results:** Only 100 and 50 mg/kg olaparib doses caused tumour regression, yet all but the lowest led to acute PAR inhibition. The differential activity factor was time over PAR Cmin,ss simulations using the mathematical model at steady state predicted a threshold where >95% reduction in PAR caused >20-fold increase in DNA SSBs. Overlaying clinical data, we saw that 400 mg bd capsule and 350 mg bd tablet doses provide con- tinuous PAR inhibition (CSS,ss > 75% upper confidence level); 100 mg bd capsule does not. Dosing schedule assessment showed PDX regression with continuous 100 mg/kg olaparib (0/10 tumours progressed by day 100). By contrast, continuous dosing at 50 mg/kg or intermittent dosing (1 wk on / 1 wk off) at 100 mg/kg resulted in 2/10 and 10/10 progressions, respectively. Treatment withdrawal upon regression led to re- growth in all cases; re-challenge at continuous 100 mg/kg was effective (9/10 regres- sions), 50 mg/kg was not (10/10). In a maintenance setting, switching to lower or inter- mittent dosing resulted in tumour response more similar to that of continuous 100 mg/kg (1/10, 2/10 and 0/10 progressions, respectively).

**Conclusions:** Discrepancy between biologically and clinically effective olaparib doses is explained by a need for continuous >95% PAR inhibition. Both the 400 mg bd capsule and 300 mg bd tablet dose, used in the ongoing clinical programme, provide this. Dosing schedule data suggest continuous PAR inhibition is also needed for long-term responses. These data highlight an important principle for treatment of patients with PARP inhibitor monotherapy.

**Legal entity responsible for the study:** AstraZeneca

**Funding:** AstraZeneca

Results: A total of 21 pts were enrolled. Stage 1: 3, 4, and 8 pts were enrolled in the 200, 400, and 600 mg cohorts. One pt in the 600 mg cohort experienced DLT [Gr3 nausea]. The most common AEs of any grade (≥30% of pts) were nausea, diarrhea, decreased appetite, vomiting, and fatigue. Cmax and AUC of ipatasertib were dose-proportional from 200 to 600 mg. Eight pts had stable disease (SD); 2 of those 8 pts continued study treatment beyond 4 months. Stage 2: 3 pts each were enrolled in the 200 and 400 mg cohorts. No DLTs were observed. The most common AEs of any grade were nausea, diarrhea, vomiting, diabetes mellitus, dysgeusia, and dizziness. Ipatasertib Cmax and AUC were similar to those in monotherapy. Of the 6 pts, complete response was observed in 1 pt and SD was observed in 1 pt. Three pts continued study treatment beyond 4 months; 2 of those 3 pts had previously received AA and enzalutamide. Biomarker results will be presented.

Conclusions: Ipatasertib was well-tolerated for Japanese pts. Based on our results, the recommended doses of ipatasertib for further development are 600 mg for monotherapy and 400 mg for in combination with AA plus prednisolone.

Clinical trial identification: JapCTI-152910, 22-May-2015

Legal entity responsible for the study: Chugai Pharmaceutical Co., LTD.

Funding: Chugai Pharmaceutical Co., LTD.


Clinical trial identification: JapCTI-152910, 22-May-2015

Legal entity responsible for the study: Chugai Pharmaceutical Co., LTD.

Funding: Chugai Pharmaceutical Co., LTD.


Background: AXL is a receptor tyrosine kinase that plays an important role in signal transduction in normal and malignant cells. Abnormal expression and/or activation of AXL can provide a survival advantage for certain cancer cells, and AXL up-regulation is associated with poor prognosis in several cancers. Recently, it has been reported that up-regulation of AXL expression is a mechanism of EGFR-TKI resistance in EGFR-mutant non-small cell lung cancer.

Methods: Kinase activity was measured by mobility shift assay. The inhibition of hGSK6-induced migration was measured in AXL-transfected NIH3T3 (NH3T3-AXL) cells. The in vivo anti-tumor effects of DS-1205b mono- and combination therapy with EGFR-TKIs were evaluated in NIH3T3-AXL allograft and HCC827 xenograft models. Protein expression was analyzed by Western blot or immunohistochemistry and gene expression was analyzed by RT-PCR or RNA seq.

Results: We found that DS-1205b selectively inhibited AXL kinase activity with IC50 of 1.3 nM, and with NIH3T3-AXL cells, DS-1205b potently inhibited the hGSK6-induced migration in vitro with EC50 of 2.7 nM. DS-1205b monotherapy exerted significant antitumor activity in an NIH3T3-AXL allograft model. In an HCC827 xenograft model, combination treatment with DS-1205b and osimertinib significantly delayed on the onset of tumor resistance compared to osimertinib alone in a manner proportional to DS-1205b dose. DS-1205b also showed a similar resistance delay effect with erlotinib combination in the same xenograft model. AXL up-regulation was associated with the development of resistance to erlotinib treatment in another HCC827 xenograft study, and DS-1205b restored the antitumor activity of erlotinib in erlotinib-resistant tumors in a dose-dependent manner.

Conclusions: In an HCC827 xenograft model of EGFR-mutant NSCLC, inhibition of AXL activity by DS-1205b restored sensitivity to erlotinib, and addition of DS-1205b to osimertinib delayed the onset of resistance to osimertinib. These findings support further non-clinical and clinical studies targeting inhibition of AXL in EGFRTm NSCLC.

Legal entity responsible for the study: Daiichi Sankyo Co., Ltd.

Funding: Daiichi Sankyo Co., Ltd.


397P Immune related adverse events (irAEs) in early phase immunotherapy (IO) trials: Implications for recommended phase 2 dose (RP2D) determination

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Background: IO agents have a unique profile of irAEs. Due to the potential of delayed severe irAEs, we examined if conventional dose-limiting toxicity (DLT) periods may underestimate the rate of clinically significant irAE (csAE), defined as an irAE that required systemic therapy, drug delay or discontinuation.

Methods: A retrospective chart review of patients (pts) on early phase IO trials at Princess Margaret Cancer Centre examined severity (CTCAE v4.0), management, timing of onset and resolution of all grade (G) irAEs. A generalized estimating equation model assessed the association between time on treatment (Rx) and csAE, adjusted for duration of IO. Potential predictors of csAEs were assessed.

Results: From 8/2012-9/2016, 239 pts across 21 trials received ≥1 dose of IO (72% single agent; 28% IO-based combination). The most common tumors were melanoma (23%) and lung (18%) cancer. Among 890 total Rx-related irAEs, 93 (10%) were csAEs, including 22 (24%) endocrine, 15 (16%) gastrointestinal (GI), 11 (12%) respiratory, 10 (11%) skin and 10 (10%) hepatic csAEs. Median onset was <90 days for hepatic, GI and general (eg fatigue) csAEs, and >90 days for endocrine, respiratory, skin and musculoskeletal csAEs (P = 0.03). One pt with G3 hepatitis and G4 hypophysitis met protocol-defined DLT criteria and 27 irAEs fulfilled DLT criteria but occurred after the DLT period. 61 pts had csAEs, with 21 (34%) having ≥1 csAE. The onset of first csAE was 0-6 weeks (wks) in 30 (49%) pts; wks 7-12 in 16 (26%); wks 13-48 in 10 (16%); and ≥49 wks in 5 (8%) pts. The odds ratio (OR) for the first csAE occurrence within first 6 wks vs ≥ 6 wks was 3.93 (95% CI 2.0-3.5, P = 0.002), accounting for varying Rx duration. After adjustment for time on Rx, csAE correlated only with response on univariate analysis (OR 4.3, 95% CI 2.1-8.9, P < 0.001), but not with single or combination IO, age, ECOG status, prior IO or prior therapy lines.

Conclusions: Risk of first-onset csAE was higher during the initial 6 wks of IO, supporting use of conventional DLT period for dose escalation decision. However, as late csAEs were also seen, RP2D determination should consider the entire temporal course of CsAE. Occurrence of csAEs positively correlated with response to IO, relative to time on Rx.

Legal entity responsible for the study: Princess Margaret Cancer Centre

Funding: None

Disclosure: M. Butler: Advisory board for: Merck, Bristol-Myers Squibb, Novartis, Turnstein, EMD Serono, Immunocore. D. Hoag: Advisory board for Roche, Bristol-Myers Squibb, Novartis, EMD Serono, Merck. N. B. Leigh: Research funding from Novartis. L.L. Siu: Research funding from Bristol-Myers Squibb, Merck, Novartis, AstraZeneca/MedImmune and Roche-Genentech. P.L. Bedard: Research funding from Novartis, Roche-Genentech, Bristol-Myers Squibb, AstraZeneca/MedImmune. All other authors have declared no conflicts of interest.
Background: The incidence and clinical significance of drug-induced electrolyte abnormalities (EAs) in phase I studies is not well documented. The objective of this study is to evaluate the incidence of EAs, graded according to CTCAE v4.03, and its correlation with factors influencing them.

Methods: A retrospective chart review was performed of 1088 cases in 82 phase 1 clinical trials consecutively treated from 2011 to 2015 at the Drug Development Unit, The Royal Marsden Hospital. Cox regression was used to examine the relationship between overall survival and baseline characteristics, treating the occurrence of grade 3/4 EAs as a time-varying covariate.

Results: The most common EAs in all grades during trials are: hypokalemia 62%, hypophosphatemia 40%, hyponatremia 32%, hypomagnesemia 17% and hypocalcemia 12%. Overall, grade 3/4 EAs occurred in 19% of cases. More specifically, grade 3/4 EAs were observed, as follow: hypophosphatemia 10%, hypophosphatemia 6%, hypokalemia 5%, hypomagnesemia 1%, hypermagnesemia 1%. Grade 3/4 EAs occurred during the dose-limiting toxicity window in 8.73% of cases. Overall, diarrhea was associated with hypomagnesemia in all grades (HR 1.78, 95% CI: 1.32-2.39, p < 0.001), with G3/G4 hypokalemia (HR 1.90, 95% CI: 1.09-3.45, p = 0.02) and hypophosphatemia in all grades (HR 0.79, 95% CI: 0.62-0.99, p = 0.008). Vomiting was also associated with hypomagnesemia in all grades (HR 1.45, 95% CI: 1.08-1.95, p = 0.01) and G3/G4 hypokalemia (HR 2.91, 95% CI: 1.62-5.23, p < 0.001). Baseline hyperalbuminemia, hypophosphatemia and female gender are associated with higher risk of developing other EAs during trial in the univariate analysis. Patients who developed G3/E4As during follow-up had a poorer median overall survival (OS) (26 weeks vs 37 weeks, HR = 1.61, 95% CI: 1.37-1.90, p < 0.001).

Conclusions: Baseline EAs are common in patients with advanced cancers participating in phase I trials. This is the first study to demonstrate the clinical significance of baseline hyperalbuminemia and hypophosphatemia, which are predictors of development of other EAs in phase I studies. G3/4 EAs are adverse prognostic factors of OS independent of serum albumin levels.

Legal entity responsible for the study: The Royal Marsden Hospital NHS Foundation Trust

Funding: None

Disclosure: J. de Bone: Consulting or advisory role: Astex, AstraZeneica, Genentech, Gennab, GSK, Merck, Pfizer, Sanofi. Research funding: AstraZeneica, Genentech, GSK, Sanofi, Janssen. U. Banerji: Receipt of grants/research supports: Astex, Karus Therapeutics, Novartis, Vernaol. All other authors have declared no conflicts of interest.

40P LCZ 696, administered during doxorubicin, trastuzumab or pertuzumab treatment, prevents cardiotoxicity in our in vitro model


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Background: Doxorubicin (DX), Trastuzumab (T) and Pertuzumab (P) are antineoplastic drugs used in the treatment of breast cancer. Adverse cardiovascular events related to anticancer drugs are among the leading causes of morbidity and mortality in cancer patients. Sunitinib-valratan (LCZ 696) is a combination drug, made up of a nephrilin inhibitor sunitinib and angiotensin II receptor blocker valsartan, used for the treatment of heart failure in patients with a reduced ejection fraction. Here, we aim to assess whether LCZ 696, administered during DX, T or P treatment, reduces in vitro anticancer drugs-related cardiotoxicity compared to Valsartan (V), used as a control drug.

Methods: The H9C2 rat cardiomyoblasts were seeded in 96-well plates at a density of 1 x 10^4 cells/well and incubated at 37°C with 5% CO2 for 16 hours. After the addition of 200 μM of T, P or DX in the culture medium, cells were incubated for 72 hours. The cells were further treated in the absence or presence of 10 μM of LCZ 696 or V for additional 3 days. Viability of cells was determined using trypan blue exclusion test and cell survival was expressed as percentage of viable cells compared to control untreated cells.

Results: LCZ 696 reduced significantly T, P and DX related toxicity in H9C2 cardio-myoblasts as evidenced by the higher percentage of viable cells treated with combinations of T, P or DX with LCZ 696 with respect to cells treated with T, P or DX alone (p < 0.001). DX significantly T and DX related toxicity in H9C2 cardiomyoblasts treated with combinations of T or DX and V with respect to the cells treated with T or DX, used as single agents (p < 0.001). However there was no significant reduction of toxicity when H9C2 cells were treated with P + V. Thus, both LCZ 696 and V reduced significantly DX and T related toxicity when administered to H9C2 cardiomyoblasts after the antiangioplastic treatment (no significant difference between LCZ 696 and V treatment, p = 0.6). Moreover, LCZ 696 was significantly more effective than V (p = 0.001) in reducing both T and P related toxicity when administered to cultures of H9C2 cardiomyoblasts after antiangioplastic treatments.

Conclusions: LCZ 696, administered during DX, T or P treatment, significantly increases the viability of treated cells, thus reducing toxicological effects of these drugs, as demonstrated by our in vitro experiments. The future perspective aims to test LCZ 696 in vivo models to assess its capability to blunt left ventricular dysfunction after antiangioplastic treatments.

Legal entity responsible for the study: Nicola Maurera

Funding: None

Disclosure: M. De Laurentiis: Advisory Board: Novartis, Roche, Pfizer, AstraZeneca, Celgene, Eisai. All other authors have declared no conflicts of interest.

401P MEK inhibitor retinopathy

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Background: To evaluate the presence and characteristics of subretinal fluid (SRF) associated with the use of MEK inhibitors in the treatment of systemic cancer MEK retinopathy is described as symmetrical bilateral disease that develops in a time-dependent and dose-dependent manner.

Methods: In this prospective, observational study, collected data from 14 patients with locally advanced or metastatic cancer undergoing treatment with the MEK inhibitor as clinical trials between 2010-2013. They underwent regular ophthalmological examinations including determination of visual function, biomicroscopy, dilated fundoscopy and optical coherence tomography (OCT).

Results: Of the 14 participants, 10 (71%) were men; the mean (SD) age was 65 years (range, 41-80 years). Six (48%) study participants developed SRF during the study period. OCT revealed subfoveal neuroretinal elevation, serous retinal detachments often asymptomatic. In general it solves spontaneously without any apparent functional deficits or changes in structural integrity, and does not require the suspension of the treatment.

Conclusions: The presence of serous retinal detachment in patients undergoing treatment with the MEK inhibitor is common. Visual symptoms were mild and mainly transient and the presence of SRF did not lead to permanent ocular disorder. It is important to investigate all previous ocular disorders and pharmacological interactions of MEK inhibitor that could associate with ocular effects.

Legal entity responsible for the study: START Madrid

Funding: None

Disclosure: All authors have declared no conflicts of interest.
standard 3 + 3 design. Starting dose (dose level 1) was 10 mg/m², 15 mg/m² and 20 mg/m² every 3 weeks. Dose-limiting toxicities (DLT) were defined as grade 4 haematological or grade 3 or 4 non-haematological toxicities. Preliminary efficacy of E-PC in pts with ADCs, defined by clinical benefit rate (CBR) (CR + PR + SD for 6 weeks or more as per RECIST), and survival were determined in the phase 2 portion.

Results: 30 pts were enrolled (P1P = 12) from Jan 2008 to Nov 2014. In the P1P, 2 DLTs (G3 gi bleeding and G3 joint pain) were experienced at dose level II, thus establishing dose level I as the MTD and RP2D. 21 pts were treated at RP2D. Baseline demographics of phase 2 portion: M:F = 9/12, Median age 54 (range 40-69), ECOG PS 0/1/2: 10/10/1. Prior lines of chemotherapy prior to the MTD were 3 (range 2-8), median cycles: 6 (range 1-19).

Common related G3 adverse events (AEs) include: (9%) neuropathy (48%), anemia (43%), thrombocytopenia (29%), mucositis (10%). Febrile neutropenia occurred in 10% (n = 2) of pts. 18 pts were evaluated for response (3 PR, 9 SD, 4 PD). CBR 77.8% (95% CI 56.8-97.5%). Median PFS and OS was 6.9 and 9.0 months (95%CI 3.5 – 7.6, 3.5 – 13.1 months) respectively.

Conclusions: E-PC administered at RP2D was well-tolerated. Comparing with prior reported series of E-PC alone, E-PC showed more favorable efficacy and has promising activity in advanced ADCs. Acknowledgement - Supported by Novartis Pharmaceuticals Ltd.

Clinical trial identification: NCT01514110

Legal entity responsible for the study: The Chinese University of Hong Kong

Funding: Novartis Pharmaceuticals Ltd.

Disclosure: H.H. Long: Research Funding: MSD. Advisory: Novartis, Roche. Travel Support: AbbVie, Roche, Mercado, Bayer, Roche-Myers-Serum, AbbVie, Bayer. Y. Ye: Advisor: Novartis, Eli Lilly. All other authors have declared no conflicts of interest.

### 403P

#### Phase I studies of the novel carcinembryonic antigen T-cell bispecific (CEA-CD3 TCB) antibody as a single agent and in combination with atezolizumab: Preliminary efficacy and safety in patients (pts) with metastatic colorectal cancer (mCRC)


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Background: CEA-CD3 TCB (RG7802, RO6958688) is a novel T-cell bispecific antibody targeting CEA on tumor cells and CD3 on T cells. Preclinically, CEA-CD3 TCB had potent antitumor activity, leading to increased intratumoral T-cell infiltration and activation, T-cell-mediated tumor cell killing and PD-L1/PD-1 upregulation.

Methods: In 2 ongoing dose-escalation phase I studies, CEA-CD3 TCB is given as monotherapy IV QW (S1) or in combination (QW) with atezolizumab 1200 mg Q3W (S2) in pts with advanced CEA positive (G3) related AEs were pyrexia (56%), infusion-related reactions (18%), grade 3 rash (4%), thrombocytopenia (29%), mucositis (10%). Febrile neutropenia occurred in 10% (n = 2) of pts. 18 pts were evaluated for response (3 PR, 9 SD, 4 PD). CBR 77.8% (95% CI 56.8-97.5%). Median PFS and OS was 6.9 and 9.0 months (95%CI 3.5 – 7.6, 3.5 – 13.1 months) respectively.

Conclusions: E-PC administered at RP2D was well-tolerated. Comparing with prior reported series of E-PC alone, E-PC showed more favorable efficacy and has promising activity in advanced ADCs. Acknowledgement - Supported by Novartis Pharmaceuticals Ltd.

Clinical trial identification: NCT01514110

Legal entity responsible for the study: The Chinese University of Hong Kong

Funding: Novartis Pharmaceuticals Ltd.

Disclosure: H.H. Long: Research Funding: MSD. Advisory: Novartis, Roche. Travel Support: AbbVie, Roche, Mercado, Bayer, Roche-Myers-Serum, AbbVie, Bayer. Y. Ye: Advisor: Novartis, Eli Lilly. All other authors have declared no conflicts of interest.

#### 404P

Dose escalation study of vemurafenib with crizotinib or sorafenib in patient with BRAF-mutant advanced cancers


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Background: BRAF inhibitors are effective in melanoma and other cancers with BRAF mutations; however, patients ultimately develop therapeutic resistance through activation of alternative signaling pathways such as MET, PDGFR and CRAF. We hypothesized that combining the BRAF inhibitor vemurafenib and MET inhibitor crizotinib or PDGFR/CRAF inhibitor sorafenib can overcome resistance.

Methods: We designed a phase I study (3 + 3 design) to determine the safety of vemurafenib (240-960 mg PO BID q 28 days) with crizotinib (250 mg PO daily or BID q 28 days) in arm A or sorafenib (200 mg PO daily to 400mg PO BID q 28 days) in Arm B in patients with BRAF-mutant advanced cancers. Endpoints included maximum tolerated dose (MTD), dose limiting toxicities (DLT), safety, response (RECIST v1.1) and plasma cell-free DNA mutation analysis.

Results: Thirty-six patients (arm A, 13; arm B, 23), median number of prior therapies (29 % had prior BRAF/MEK inhibitors) were treated. Patients (melanoma 17/36, 47%; papillary thyroid cancer 3/36, 8%; lung adenocarcinoma 2/36, 6%; other 9/36, 25%) had BRAFV600E (30), V600K (3) or other BRAF mutations (3). Vemurafenib 240mg BID with crizotinib 250mg BID in 14 patients experienced DLTs with vemurafenib 720 mg BID with sorafenib 400mg/200mg were identified as MTDs. DLTs included grade (G) 3 rash (2) in arm A and G3 rash and G3 hypertension in arm B. Other G3 treatment related toxicities were G3 fatigue (2), G3 anemia (1), G3 thrombocytopenia (1), G3 neutropenia (1), G3 thrombembolic event (1) in arm A and G3 hypertension (1), G3 headache (1), G3 diarrhea (2), G3 intracranial inflammation (1) in arm B. In Arm A, 3 of 13 (23%) patients (melanoma refractory to BRAF monotherapy [2] and...
Hepatic functional imaging and genomics to predict irinotecan pharmacokinetics and pharmacodynamics: The PREDICT IR study

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20%) predicted by Methylene tetrahydrofolate reductase (MTHFR) 677C

(P < 0.05).

2) Grade 3 diarrhea (N = 4, 13%) predicted by SN38 AUC(0-407)P < 0.04).

Results: 12 pts analyzed, 31 pts completed 4 cycles. (1) PK correlates: (a) HNJ CL and hIRhET with SN38 Metabolic CL (P < 0.04) and (b) HNJ DLCl with IR AUC(0-407)P < 0.04). (2) Grade 3 + diarrhea (N = 4, 13%) predicted by SN38 AUC(0-16)P < 0.04, (a) and Metabolic CL (P < 0.04), and gene variants for SCLC2A2 and -8A3, ABC2, UGT2B7, CYP3A4C and DPYD (P < 0.003) (3) Grade 3 + neutropenia (N = 9, 28%) predicted by SN38 PK exposure (P < 0.02), HNJ CL and hIRhET (P < 0.0001) and variants for SLC7A7, SLC22A2, CHST1, UGT1A1, ~287, ABCB1. (4) ORR (N = 6, 20%) predicted by Methylene tetrahydrofolate dehydrogenase (MTHFR) 677C > T (P = 0.002), SN38 exposure (P < 0.003), and variants in metabolic/transporter genes (P < 0.03).

Conclusions: Hepatic functional imaging with extensive pharmacogenomics correlated with Irinotecan PK and PD enabling the future development of nomograms to individualize its dosing. Clinical trial identification: Australian Clinical Trials Registry: ACTRN12610080983055

Legal entity responsible for the study: Peter MacCallum Cancer Centre

Funding: Australian Federal Government: National Health and Medical Research Council Project Grant

Disclosure: All authors have declared no conflicts of interest.
Background: The RHM score has been validated to predict survival in different populations of patients starting phase I clinical trials. Most of the populations where it has been validated are of heavily treated patients that lack other treatment options. The type of phase I trials is changing and we aimed to validate the score in a new cohort with more patients treated on an early line, rather than the usual classic phase I trials heavily pretreated patient population.

Methods: We analyzed the RHM score in the patients treated in our center in a phase I trial between 2012 and 2017. We collected demographics data, overall survival after starting the trial, the RHM score (albumin, LDH, and number of metastatic sites) for all patients and the treatment line. We considered a late line anything over two treatment lines and in any case if the patient did not have any other treatment available depending on the tumor type. An early line was the first or second treatment line when the patient did have further lines available.

Results: We treated 77 patients on a phase I trial in our institution, 23 males and 54 females. Mean age was 55 years (26-77). RHM score was 0 (1/25) in (31/23020) patients. Thirty-three patients were treated on an early line. Median survival for low score (0/1) was 639 days and for high score (2/3) was 327 days p=0.0834. The mean survival for patients with low RHM score was higher than those with a high RHM score in every treatment line, although due to the low number of patients in some of those categories the difference was not significant.

Conclusions: The RHM score did predict well the overall survival in our patients. The survival times in our institution are higher than those previously published, probably due to the inclusion of the tumor type on earlier treatment lines than those used before to calculate and validate the score. Our findings support the use of the RHM score for the selection of patients entering phase I trials irrespective of the design of the trial (early vs. late line).

Legal entity responsible for the study: Medical Oncology Department, Hospital General Universitario Gregorio Marañón.

Funding: Instituto de Investigación Sanitaria Hospital Gregorio Marañón

Disclosure: All authors have declared no conflicts of interest.

References

408P Validation of the Royal Marsden Hospital (RHM) prognostic score on an enriched early treatment line cohort for phase I trial patients


Medic Oncology, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón (ISGOM), Madrid, Spain

Conclusions: These results provide experimental evidence that more efficient and complete EGFR blockade may determine better tumorantumor activity and could contribute to prevent and/or overcome acquired resistance to EGFR inhibitors.

Legal entity responsible for the study: Universidade degli studi della Campania, “Luigi Vanvitelli”

Funding: Associazione Italiana per la Ricerca sul Cancro (AIRC)

Disclosure: All authors have declared no conflicts of interest.

Phase I study of the investigational, oral pan-RAF kinase inhibitor TAK-580 (MN24840) in patients with advanced solid tumors (ST) or melanoma (MEL): Final analysis


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Background: MAPK pathway mutations leading to signaling hyperactivation are common in many ST, as RAF kinases play a key role in MAPK signaling, they represent a valid target for therapy. As a pan-RAF inhibitor, TAK-580 is differentiated from other platforms. Adverse events (AEs), objective response rate (ORR), and disease control rate (DCR: CR + PR + SD) were assessed.

Results: Twenty-four pts in Part 1 and 113 pts in Part 2 were enrolled. 24 of 113 pts were HER2 expressing solid tumors other than BC and GC. DS-8201a was administered up to 8 mg/kg in Part 1 and dose level of 6 mg/kg IV every 3 weeks was chosen. DLTs were not observed in the study. In the updated Part 1 results, confirmed ORR was 35%, DCR was 91% (BC: 88%, GC: 100%), and the median duration of treatment was ≥22 weeks in heavily pretreated BC and GC pts. Non-BCC and non-GC cohort consists of 11 CRC, 5 NSCLC, 4 salivary gland, 2 Paget’s disease, 1 cholangiocarcinoma and 1 esophageal cancer. ORR including under confirmation and DCR were 33% and 91%, respectively in evaluable 12 pts. Two out of 5 evaluable pts with CRC and 2 out of 4 evaluable pts with salivary gland achieved PRs. Of all pts in this phase 1 study, the most common AEs of any grade were nausea (≥Gr 4 60%), ≥Gr 3 23%), decreased appetite (≥Gr 4 35%, ≥Gr 4 4%), vomiting (≥Gr 3 30%, ≥Gr 3 0%) and platelet count decreased (≥Gr 3 90%, ≥Gr 3 99%). Updated phase 1 results will be presented.

Conclusions: DS-8201a was well tolerated and is remarkably active in pts with heavily pretreated HER2 expressing BC and GC with durable disease control. Promising efficacy in HER2 expressing other tumors was observed and warrants further investigation.

Clinical trial identification: NCT02564900

Legal entity responsible for the study: Daiichi Sankyo CO., LTD.

Funding: Daiichi Sankyo CO., LTD.

approved BRAF-specific RAF inhibitors. Here we report the expanded cohort data from a single-agent, first-in-human study of TAK-580 (NCT01425008).

**Methods:** Patients with advanced or inoperable stage III/IV ME liver metastases (n=10) from the leading European and US centers were enrolled. The study comprised two dose groups: a 140 mg dose group (50 patients) and a 210 mg dose group (50 patients). The primary endpoints included the incidence of grade 3 or 4 adverse events (AEs), clinical responses, and spleen metastases. The secondary endpoints included the incidence of grade 3 or 4 AEs, changes in tumor size, and changes in the number of liver metastases. The study was terminated due to the lack of clinical activity at the higher dose level.

**Conclusions:** The use of TAK-580 in patients with advanced or inoperable stage III/IV liver metastases was limited due to the lack of clinical activity at the higher dose level. Therefore, further clinical development of TAK-580 in this patient population is not warranted.

Legal entity responsible for the study: Takeda Pharmaceutical Company Limited

Disclosure: A.J. Ozananski: Consulting or advisory role: Merck, Takeda, BMS, Kynko Kakko Kirin, G1 Therapeutics; Research funding: Takeda, ImmunoGen, EMDC, Serono, Amgen, Incyte, Kynko Kakko Kirin, Lilly, Advaxis, Mirati Therapeutics, Ignoto, Novartis, Pfizer, BMS, Kura; Travel/accommodation/expenses: Takeda, Churchill Pharmaceuticals, Kynko Kakko Kirin, G1 Therapeutics. R. Gonzalez: Consultant: Bristol-Myers Squibb, Novartis, Genentech. Research support: Merck, Novartis, Genentech, Bristol-Myers Squibb, Incyte, Syndax, Takeda. P. Corrie: Advisory boards; Novartis, Pierre Fabre, Bristol-Myers Squibb, MSD. Celgene. Research funding: Celgene. Speaker honoraria: MSD, Novartis. M. Middiott: Consulting or advisory role: GSK, BMS, Amgen, Merck, Roche (all compensated); Celgene. Speaker honoraria: (both uncompensated); Travel/accommodation/expenses: Roche, Merck: Corporate-sponsored research; GSK, AZ, Eisai, Clovis, BMS, Amgen, Roche, Merck, Vertex, ImmunoGen, Pfizer, Medimmune. P. Lorigan: Advisory board: GSK, Novartis, Roche, Bristol-Myers Squibb, Merck, Amgen. Travel: Corporate-sponsored research; Bristol-Myers Squibb, MSD. A. Daed: Stock ownership: OncoSec, Inc.; Advisory board or board of directors: Novartis, Merck, Pfizer, Genentech, Corporate-sponsored research: Merck, Pfizer, Genentech, BMS, S. Zhang, E. Haberman: Employment: Millennium Pharmaceuticals, Inc. B. Bahamon, L. Rangachari, M. Kreisler: Employment, Millennium Pharmaceuticals, Inc. D. Rosco: Corporate-sponsored research: Takeda Oncology. All other authors have declared no conflicts of interest.

**411P** Pharmacological activity of CB-103: An oral pan-NOTCH inhibitor with a novel mode of action

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**Background:** NOTCH signalling is a developmental pathway known to play critical roles during embryonic development as well as for regulation of self-renewing tissues. Aberrant activation of NOTCH signalling leads to deregulation of the self-renewal process resulting in sustained proliferation, invasion and metastasis, all of which are hallmarks of cancer. When the NOTCH pathway is inappropriately activated by genetic lesions (over expression of NOTCH ligands/receptors, GOF mutations in NOTCH receptors as well as chromosomal translocations), it becomes a major driver for NOTCH-dependent cancers and resistance to standard care. Several therapeutic approaches have been utilized to block NOTCH signalling, e.g. a) the use of monoclonal blocking antibodies (mAbs) against NOTCH ligands and receptors and b) the use of small molecule gamma-secretase inhibitors (GSIs). Here we report the pharmacological characterization of CB-103, a first-in-class orally-active small molecule, protein-protein interaction inhibitor of the NOTCH transcriptional activation complex.

**Methods:** Primary pharmacodynamic (PD) studies were conducted to investigate CB-103 in relation to its desired therapeutic effect for treating advanced or metastatic hematological and solid tumour malignancies as NOTCH pathway inhibitor. Regarding the PD effect, in vitro studies demonstrated for CB-103 a dose-dependent decrease in NOTCH signalling activation with a unique mechanism compared to GSIs and mAbs. In a panel of > 120 cell lines of various malignancies CB-103 was active on a subset of 24 cancer cell lines, including different solid tumours (breast, lung, sarcomas), lymphomas and leukemias.

**Results:** Moreover, CB-103 demonstrated anti-NOTCH1 activity in the Triple-Negative Breast Cancer HCC1957 cell line, being resistant to GSIs due to a NOTCH2 chromosomal translocation. In addition, CB-103 exhibited anti-tumour efficacy in multiple in vivo models and patients derived xenograft models.

**Conclusions:** Safety pharmacology and toxicology studies have been completed and revealed an excellent non-clinical safety profile of CB-103. A first-in-human Phase I/II clinical study in advanced solid tumours and haematological malignancies is under preparation.

Legal entity responsible for the study: Cellensis Biotech AG

Disclosure: D. Weber: Chief Medical Officer of Cellensis, co-founder, stock ownership. R. Lehal: Chief Scientific Officer, co-founder, stock ownership. J.-P. Bourquin: Medical advisory board Cellensis. M. Bauer: Chief Executive Officer, co-founder, stock ownership. M. Munroe: Chief Operating Officer, co-founder, stock ownership. F. Radtke: Chairman of the Board, co-founder, stock ownership. All other authors have declared no conflicts of interest.

**412P** Design and development of potent E1 ubiquitin activating enzyme inhibitor, CPL-410-005, as a novel anticancer therapy

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**Background:** The ubiquitin-proteasome system is crucial in tumorogenesis. The division rate of cancer cells, thus protein synthesis, is increased in comparison to normal ones, what sensitizes tumors for any protein changes. Proteasome inhibitor - bortezomib was the first inhibitor registered in treatment of blood cancers. However, drugs beneficial for solid tumors are still missing. Therefore targeting of E1 enzyme as a start of UPS pathway may serve as a promising anticancer therapy.

**Methods:** We have designed a novel small molecule inhibitor, CPL-410-005. The inhibitory potency of compound was assessed on purified E1 enzyme, using biochemical assay. Assays to measure cellular polubiquitinylation or ubiquitin-like modifications level were developed. The compound’s biological activity and selectivity was evaluated in a number of cancer cells using cell viability assays, Western Blot and flow cytometry, analyzing programmed cell death, unfolded protein response or cell cycle inhibition.

**Results:** CPL-410-005 inhibits E1 enzyme with greater potency than MLN7243. This results in cellular polubiquitinylation inhibition, while the impact on other ubiquitin-like modifications (neddylation, sumolation, simulation) is minor. Tumor proliferation rate inhibition was pronounced in reference to the non-malignant cells [IC50 values of 20 nM for HTCT116 cells vs IC50 values of 400 nM for HEK293 cells]. Moreover, a higher level of unfolded protein response or programmed cell death was observed in cells treated with CPL-410-005 in reference to MLN7243 (3% apoptotic cells vs 30% for MLN7243 vs CPL-410-005, respectively). In case of CPL-410-005, apoptosis rate was higher in tumor than in normal cells (80% apoptotic cells vs 20%, respectively). A high throughput study was performed, to determine the activity of CPL-410-005 on 120 human tumor cell lines, showing that > 85% tested cell lines responded with IC50 value below 100nM. The initial in vivo studies on tumor human xenografts are ongoing.

**Conclusions:** We have designed and evaluated in vitro a potent E1 inhibitor - CPL-410-005, which shows promising in vitro activity. Further preclinical studies are necessary to develop this compound as a novel anticancer therapy.

Legal entity responsible for the study: Celon Pharma


**413P** RX 3117, a novel hypomethylating agent, shows promising therapeutic activity in combination with nab-paclitaxel and checkpoint inhibitors in preclinical models

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**Background:** A novel nucleoside analogue, RX-3117, is being evaluated in a Phase IIa study in patients with advanced pancreatic and bladder cancer. RX-3117 shows promising antitumor activity in xenografts including patient-derived xenografts resistant to gemcitabine. Here we demonstrate the preclinical effects of combination therapy with RX-3117 + Abraxane or anti-PD1 immunotherapy.

**Methods:** One colorectal (MC84), pancreatic (Pan02) syngeneic xenograft and patient-derived pancreatic (CTG-0723) xenograft model were exposed to 60 mg/kg RX-3117, followed by a second cycle of RX-3117 + Abraxane, i.e. MC84 tumor infiltrating lymphocytes were measured at days 5 and 12 with RX-3117.

**Results:** In MC84 at day 28, RX-3117 or anti-PD1 showed TGI of 99% and 93% whereas the combination showed 99% TGI. Differences were also observed in TILs.

**Conclusions:** We have designed and evaluated in vitro a potent E1 inhibitor - CPL-410-005, which shows promising in vitro activity. Further preclinical studies are necessary to develop this compound as a novel anticancer therapy.
Relative to vehicle (CD4+:10.6+/−1.6, CD8+:8.6+/−1.1, %CD4+:17.4+/−1.4 and CD8+: cells (12.3+/−1.1 increased. %MDSCs decreased on Day 5 in blood (42+/−7.7 vs 29+/−6). %CD8+ increased (9.6+/−3.3 vs 12.3+/−3.2) and %MDSC decreased (15.4+/−3.7 vs 10.6+/−3.3) in tumor on Day 12. In Pan02, RX-3117 + anti-PD1 resulted in a day 52 TGI of 60%. Anti-PD1 alone had a day 32 28% TGI. In CTG-0723, the first cycle of RX-3117 at 10, 30 and 60 mg/kg produced TGI of 33%, 46% and 77%. The second cycle, RX-3117 + Abraxane, day 46 TV showed TGI of 53%, 38% and 89%. Conclusions: We demonstrate the antitumor effect of RX-3117 as a single-agent and in combination with Abraxane or anti-PD1. The combination of RX-3117/anti-PD1 in MC38 produced tumor-free survivors out of 10 compared to 2 of 10 by anti-PD1 alone, indicating RX-3117 may mobilize the right population of lymphocytes to enable anti-PD-1 to work more effectively. In Pan02, RX-3117 exhibited better TGI than anti-PD-1. In CTG-0723, the combination of RX-3117 and Abraxane showed additive TGI. These studies demonstrate the therapeutic potential of RX-3117 in multiple cancers and validate the combination of RX-3117 with anti-PD-1 for further development.

Legal entity responsible for the study: Rexahn Pharmaceuticals, Inc.

Funding: Rexahn Pharmaceuticals, Inc


E. Benaim: Officer at Rexahn Pharmaceuticals, employer, stockholder.

414P A phase Ib trial of JX-594 (Pexa-Vec), a targeted multimechanistic oncolytic vaccinia virus, in combination with low-dose cyclophosphamide in patients with advanced solid tumors

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Background: JX-594 (Pexa-Vec) is a targeted oncolytic vaccinia virus designed to se- lectively replicate in and destroy cancer cells with epidermal growth factor receptor (EGFR)/ras pathway activation. Direct oncolysis plus GM-CSF expression is accompa- nied by tumor vascular disruption and anti-tumoral immunity. JX-594 was well- tolerated intravenously (IV) and intratumorally (IT). Given the immunomodulatory effects of low-dose cyclophosphamide (CP), anti-tumor synergy is predicted with JX-594. Methods: CP was delivered orally at the dose of 50 mg BID one week on one week off. JX-594 was administered day 8 of each cycle of 28-cycle PI. Five dose levels of JX-594 were explored: 3.108 and 1.109 plaque forming units (pfu). The primary objective of the study was to determine the safety of JX-594 in combination with low-dose CP in pa- tients with advanced solid tumors. Secondary objectives include response rates, PFS, pharmacokinetics and pharmacodynamics.

Results: Ten patients entered the study. 9 were evaluable for safety. No dose limiting toxicity was observed. The combination regimen was well-tolerated. The most frequent adverse events were grade 1-2 fever/transient flu like symptoms (n = 10), grade 1-2 nausea (n = 5), grade 1-2 asthenia (n = 4) and grade 1-2 fatigue (n = 4). 2 patients (breast cancer, ovarian cancer) had stable disease as best overall response. Conclusions: JX-594 + low-dose CP was well tolerated in combination with low-dose CP. PK and PD (immunological profiling) will be presented at the meeting. Two phase 2 studies are ongoing in patients with advanced HER2 negative breast cancer and advanced soft-tissue sarcomas, respectively.

Clinical trial identification: NCT02693968

Legal entity responsible for the study: Institut Bergonie

Funding: INCA

Disclosure: All authors have declared no conflicts of interest.

415P Population pharmacokinetic analysis of OT-101 (trabedersen) in patients with advanced tumors

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Background: OT-101 (Trabedersen) is a phosphorothioate anti-sense oligodeoxynu- cleotide specifically inhibiting the expression of transforming growth factor-beta 2 (TGF-β2), whose overexpression is a pivotal factor for malignant progression in solid tumors. In the clinical Phase I/II study, plasma pharmacokinetic (PK) profile of OT-101 administered intravenously was evaluated in patients with advanced tumors. A population PK model was built to further understand the factors contributing to the variability in PK of OT-101.

Methods: A total of 61 patients with pancreatic cancer (n = 37), malignant melanoma (n = 19), or colorectal carcinoma (n = 5) were treated with OT-101 with escalating doses in 2 treatment schedules (1st schedule: 7-doses-on/7-doses-off, 2nd schedule: 4-doses-on/10-doses-off; up to 10 cycles). The plasma concentration data of OT-101 were analyzed using nonlinear mixed-effect modeling (Phoenix NLME 7.0). The influence of age, gender, body mass index (BMI), body weight (BW), cancer type, treatment schedule, creatinine clearance (CrCl) and estimated glomerular filtration rate (eGFR) as covariates on PK was evaluated.

Results: With exclusion of protocol deviations, the final analysis dataset contained 92 patient cycles and 1188 plasma samples. Twenty-six patient cycles were from 7-days-on/10-days-off schedule and 66 were from 4-days-on/6-days-off schedule. The concentration-time course of OT-101 was best described by two-compartment model with combination of additive and multiplicative error. The estimates of PK parameters were as follows: central volume of distribution, Vc = 3.7 L; inter-compartmental clearance, K12 = 2.0 mL/min; distribution volume of the peripheral compartment, V2 = 5965.83 L. eGFR were identified as the covariates on OT-101 central and peripheral compartment, with K12 = 11.45. Significant increase in systemic exposure of OT-101 was observed with increasing eGFR.

Conclusions: The PK profile of OT-101 was best described by a two-compartment model. The model will be used with the sparse PK samples collected from the planned phase 3 clinical trial to calculate exposure measures for use in subsequent PK/PD analysis.

Legal entity responsible for the study: Oncotelic

Funding: None


A phase 1 study of oral LOXO-292 in adult patients with advanced solid tumors, including RET-fusion non-small cell lung cancer, medullary thyroid cancer and other tumors with increased RET activity

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Background: RET is a receptor tyrosine kinase with critical roles in normal physiology. Fusions of the RET kinase with a partner protein have been identified in ~2% of non- small cell lung cancers (NSCLC) and a subset of papillary thyroid cancers and other tumors. RET mutations occur in the majority of medullary thyroid cancers (MTC). Although multikinase inhibitors with anti-RET activity are in the clinic, their activity is limited by incomplete RET inhibition in patients, toxicity from off-target effects (e.g. VEGFR2) and poor pharmacokinetics (PK). LOXO-292 is a potent and specific inhi- bitor of RET, including fusions, activating mutations and potential acquired resist- ance mutations, with minimal inhibition of off targets, including > 100-fold selectivity for VEGFR2.

Trial design: This is an open label, multi-center, dose escalation and expansion Phase 1 study in adult patients with advanced solid tumors. Major eligibility criteria for dose esca- lation include prior cancer treatment (prior treatment with anti-RET TKIs allowed) and normal hematopoietic and major organ function. During dose escalation, when a dose level is achieved that is safe and consistent with RET target engagement, enroll- ment will be limited to patients with RET-fusion NSCLC, MTC and other tumors with RET alterations or increased RET activity, as identified in tumor or blood by prior mo- lecular assays performed locally. Once the Maximum Tolerated Dose (MTD) or recom- mended dose for further study is identified, patients will be enrolled to one of five dose expansion cohorts, depending on tumor type (i.e. NSCLC, MTC, other cancer), prior TKI therapy and type of RET alteration. The starting dose of LOXO-292 is 20 mg orally once per day, and dose escalation is proceeding using a 3 + 3 design. The primary end- point is establishment of the MTD/recommended dose for further study. Key secondary endpoints include: safety and tolerability, PK parameters and preliminary assessment of anti-tumor activity. Patients undergo safety, clinical and PK assessments and radiographic evaluation for their disease at regular intervals.

Clinical trial identification: Treatment of patients has begun. The study has been sub- mitted to the NIH (https://clinicaltrials.gov) and the ClinicalTrials.gov Identifier is pending and will be provided as soon as available.

Legal entity responsible for the study: Loxo Oncology

Funding: Loxo Oncology

Disclosure: S. Smith, T. Eary, S. Cruckshank, M. Nguyen, S. Rotherenberg: Ownership interest in Loxo Oncology. All other authors have declared no conflicts of interest.
Background: Neurotrophin ligands and their receptors TRKKA, TRKB, and TRKCC (encoded by NTRK1, NTRK2, and NTRK3) are important for growth regulation, differentiation, and survival of neurons. Translocations involving the NTRK1/2/3 kinase domain have been described in a broad range of adult and pediatric tumors, including infantile fibrosarcoma (IFS), spindle-cell sarcoma, congenital mesoblastic nephroma, pediatric papillary thyroid cancer, high- and low-grade gliomas and Ph-like acute lymphoblastic leukemia. Larotrectinib is the first small-molecule selective inhibitor of TRKA, -B, and -C in clinical development and has demonstrated tumor growth inhibition in preclinical models and clinically meaningful and durable responses in patients with NTRK-translocated cancers in an adult phase 1 trial.

Trial design: We have initiated an open-label, multi-center, international Phase 1/2 study with larotrectinib in pediatric patients with solid tumors and primary CNS tumors. A pediatric recommended phase 2 dose of 100mg/m² (capped at 100mg BID) has been established. Enrollment to phase 2 began in April 2017 and is ongoing. For the phase 2 component, patients from 1-month of age with an IFS or an NTRK-fusion positive tumor, including those who have not undergone definitive surgery are eligible. Patients who have not undergone definitive surgery are eligible as well. Larotrectinib is administered as an oral liquid formulation or capsules twice daily on a continuous 28-day cycle. Patients who have not undergone definitive surgery are eligible as well. Patients with NTRK-translocated tumors and measurable disease into three cohorts: 1) infantile fibrosarcoma; 2) other extracranial solid tumors; and 3) primary CNS tumors. The primary endpoint is objective response rate, with duration of response and progression-free survival as secondary efficacy endpoints. Data on quality of life measures and cDNA are being collected at endpoints. Each phase 2 cohort will enroll in a single stage of up to 10 patients. Molecular abnormalities will be characterized through the analysis of archival tissue.

Clinical trial identification: NIH: NCT02637687; EudraCT #: 2016-003498-16

Legal entity responsible for the study: Loxo Oncology, Inc.

Funding: Loxo Oncology, Inc.

Disclosure: M.C. Cox: Employee and stockholder of Loxo Oncology, Inc. All other authors have declared no conflicts of interest.

Chemosensitization of carboplatin by NOX66: Pharmacokinetics and safety

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Background: The experimental anti-cancer drug, idronoxil, is a selective inhibitor of P38/Akt in tumor cells, with studies showing it to be a potent chemosensitizing agent of carboplatin, in vitro and in animal studies across a wide range of cancer types. These results, however, have not translated to clinical efficacy, with a Phase 3 study of combined oral idronoxil and intravenous carboplatin in patients with late-stage platinum-refractory ovarian cancer discontinued with no efficacy seen. This lack of efficacy is now thought to be due to complete conversion of idronoxil to bio-inactive Phase 2 metabolites. NOX66 is a suppository formulation of idronoxil designed to protect the drug from Phase 2 metabolism. This first-in-human study will look at the ability of NOX66 to deliver relatively high levels of idronoxil in a bio-active form, investigating (a) PK and (b) safety of NOX66 administration both as a monotherapy and in combination with carboplatin.

Trial design: This is an open label, Phase 1 PK and safety study of NOX66 as a monotherapy and in combination with carboplatin. Patients included have end stage, refractory solid tumours, and no further therapy options available. A total of 16 patients will be recruited into the study in two cohorts of 8 patients. NOX66 suppositories are formulated using 400mg of idronoxil per 2.2g suppository. Patients are allocated to receive either one or two suppositories per day. Study Part 1: NOX66 PK: Patients receive NOX66 for 14 consecutive days as monotherapy, with a follow up period of 7 days post-dosing. Blood samples will be collected throughout the monotherapy arm to measure levels of idronoxil. If no significant adverse events are noted in this 21 day period, a patient will continue in the study. Study Part 2: NOX66 plus Carboplatin: Patients receive NOX66 at the same dose as in Part 1, for 7 days. Carboplatin is administered on Day 2 of treatment. Up to 6 cycles of chemotherapy are administered, with intervals of 28 days. For Cycles 1-3, low dose (AUC4) carboplatin is administered. Subject to safety review, standard dose (AUC6) carboplatin is administered for cycles 4-6. Safety assessment is continued throughout the study, with measures to identify efficacy signals (CT scan, ECOG) performed at baseline and after Cycles 3 and 6.

Clinical trial identification: Trial Protocol Number: NOX66-001A Clinicaltrials.gov NCT02941523

Legal entity responsible for the study: NovoXpharm Limited

Funding: NovoXpharm Limited

Disclosure: I. Minns: Employee of NovoXpharm Limited. G. Kelly: Member of the board of Directors, employee and a shareholder of NovoXpharm Limited.

Cohort 1 Platinum-sensitive high grade epithelial, non-mucinous, ovarian cancer, fallopian cancer or primary peritoneal cancer with either known deleterious or suspected deleterious germline or somatic BRCA1/2 mutation or with DNA HRD

<p>| Table: 420TIP |</p>
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<th>Treatment arm</th>
<th>Tumor type</th>
<th>Estimated sample size</th>
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<tr>
<td>Cohort 1</td>
<td>Platinum-sensitive high grade epithelial, non-mucinous, ovarian cancer, fallopian cancer or primary peritoneal cancer with either known deleterious or suspected deleterious germline or somatic BRCA1/2 mutation or with DNA HRD</td>
<td>20</td>
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<tr>
<td>Cohort 2</td>
<td>Triple negative breast cancer with either known deleterious or suspected deleterious germline or somatic BRCA1/2 mutation or with DNA HRD</td>
<td>20</td>
</tr>
<tr>
<td>Cohort 3</td>
<td>Metastatic castration-resistant prostate cancer with either known deleterious or suspected deleterious germline or somatic BRCA1/2 mutation or with documented HRD</td>
<td>20</td>
</tr>
<tr>
<td>Cohort 4</td>
<td>Extended stage small cell lung cancer who have been treated with &lt;2 prior regimens</td>
<td>20</td>
</tr>
<tr>
<td>Cohort 5</td>
<td>Gastro or gastroesophageal junction cancer who have been treated with ≤2 prior regimens</td>
<td>20</td>
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</tbody>
</table>
of TMZ administered once daily (QD) either on Days 1-7 (Arm A) or continuously (Arm B) of each 28-day cycle. The phase 2 component will further evaluate the safety, tolerability and antitumor activity of the recommended combination dose and schedule in adults with metastatic or locally advanced unresectable solid tumors (Table). Enrolment into these expansion cohorts will occur simultaneously and independent of each other. Subjects will continue to receive treatment in 28-day cycles until confirmed disease progression, intolerable toxicity, or discontinuation/withdrawal.

Legal entity responsible for the study: Beigene Ltd.

Funding: Beigene Ltd.

Disclosure: M. Johnson: Research funding compensation for consultation to the institution from OncoMed, BerGenBio, Lilly, and various Pharm/Biotech companies. Spouse is a consultant to AstraZeneca for Astellas. B. Orosz: Employee and stock holder of Beigene USA. R. Brachmann: Employee of Beigene USA. M.D. Galsky: Consulting fees from Genentech, Merck, Novartis, Astellas, AstraZeneca, and Bristol-Myers Squibb outside the submitted work; stock options in Dual Therapeutics outside the submitted work.

421TP

Phase 1b/2 study to assess the clinical effects of BGB-290 in combination with radiation therapy (RT) and/or temozolomide (TMZ) in patients with first-line or recurrent/refractory glioblastoma

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Background: Poly (ADP-ribose) polymerase (PARP) proteins are a family of DNA binding and repair proteins and are thought to play a key role in the base excision repair of DNA damage generated by TMZ. In glioblastoma (GB) cells, pharmacological modulation of PARP activity increased growth inhibition induced by TMZ in both p53-wild type and mutant GB cells lowering the TMZ IC50. RT used in the clinical treatment of GB generates mostly single-strand breaks (SSBs). In non-replicating cells PARP inhibition only delays the repair of SSBs induced by radiation with a minimal impact on cell survival. On the contrary, PARP inhibition markedly enhances radiosensitivity of proliferating cells generating double-strand breaks. Thus, PARP inhibitors have the potential to increase the therapeutic index of RT by increasing DNA damage mainly in highly replicating tumor cells, but sparing non-cycling normal tissues. BGB-290, a potent and selective inhibitor of PARP1/2, has demonstrated potent PARP trapping, brain penetration and antitumor activity in preclinical intracranial xenograft models.

Trial design: This open-label, dose-escalation/dose-expansion Phase 1b/2 study was designed to determine the safety, tolerability, pharmacokinetics, pharmacodynamics, and antitumor effects of BGB-290 at the recommended Phase 2 dose (60 mg PO BID) in combination with RT and/or TMZ. The Phase 1b component will consist of 3 dose-escalation arms. Arm A: BGB-290 will be combined with RT in patients with first-line unmethylated GB; Arm B: BGB-290 will be combined with both TMZ and RT in patients with first-line unmethylated GB; Arm C: BGB-290 will be combined with increasing doses of TMZ in patients with recurrent/refractory methylated or unmethylated GB. Once a recommended Phase 2 regimen has been established, up to 60 patients may be enrolled in the dose-expansion (Phase 2) cohort for that arm. In Arm C, 2 expansion cohorts with up to 60 patients each may be opened: 1 for unmethylated GB and 1 for methylated GB.

Legal entity responsible for the study: Beigene Ltd.

Funding: Beigene Ltd.

Disclosure: P. Wen: Grants, personal fees, and/or non-financial support from Agios, Angiogenesis, AstraZeneca, Genentech/Roche, GlaxoSmithKline, Immunocellular Therapeutics, Karyopharm, Merck, Novartis, and other biotech/pharmaceutical companies outside submitted work. D. Schiff: Grants from Cavoion & Cellxide, personal fees from VBI, Orosz, Monteris, Genentech-Roche, Heron Pharmaceuticals, Midatech, and OxiGene, outside the submitted work. R. Brachmann: Employee of Beigene USA, Inc. R. Weitzman: Consultant to Beigene, T. Cloughesy: Personal fees from Pfizer, Toogen, Roche, Novocure, Nektar, VBL, ABBVIE, Upshire Smith, Notable Labs, OxiGene, NewGen, Agios, Cortice, MedQia, PhDNa, and other pharma/biotech companies, outside the submitted work. All other authors have declared no conflicts of interest.

423TP

The first-in-human, dose-finding PROCCLAIM-CX-072 trial to assess the antitumor activity and tolerability of the prodrug therapeutic CX-072 as monotherapy and in combination with ipilimumab or vemurafenib in solid advanced tumors and lymphomas


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Background: CX-072 is a novel recombinant Probody™ drug conjugate (PDC) derived from a humanized monoclonal antibody (mAb) against CD166 and conjugated to N-succinimidyl 4-(2-pyridyldithio)-butane-N2- deacetyl-N2-4-(mercapto-4 methyl-1-oxopentyl)-mazainidine (SPDB-DM4, licensed from Immunogen), a potent microtubule inhibitor. PDCs are fully recombinant mAbs prodrugs designed to remain inactive until they are cleaved into an active mAb by tumor-associated proteases. This tumor-specific activation allows PDCs to target highly and homogeneously expressed tumor antigens while avoiding binding to these same targets on healthy tissue. An example is CD166 (also referred to as activated leucocyte cell adhesion molecule [ALCAM]), which is highly expressed in multiple cancers but also in healthy tissue. In preclinical studies, CX-09X exhibited antitumor activity and reduced peripheral binding compared to the corresponding anti CD166 ADC.

Trial design: PROCCLAIM-CX-072 (PRObody Clinical Assessment In Man) is an open-label, multicenter, dose-escalation study to determine the maximum tolerated dose (MTD) and the recommended phase 2 dose (RP2D) of CX-09X in 7 selected tumor types with high CD166 expression (breast, lung, prostate, ovarian, endometrial, head and neck, and biliary carcinomas). Part A (n ≤ 50) will initiate with accelerated dose titration, followed by a standard 3+3 design to determine the MTD and ending in a modified toxicity probability interval 2-design cohort treated at the MTD to determine the RP2D. Part B of the study will be a dose expansion phase testing CX-09X administered at the RP2D in the same 7 tumor types (up to 14 patients each, n ≤ 98). Eligibility is based on confirmed refractory metastatic or locally advanced unresectable tumor. Outcome measures include assessment of safety, tolerability, pharmacokinetics, and efficacy based on RECIST 1.1. Exploratory biomarkers will characterize tumor CD166 expression and mitotic markers as well as CX-09X activation in tumors versus peripheral blood.

Clinical trial identification: NCT03149549

Legal entity responsible for the study: CytoX Therapeutics, South San Francisco, CA, USA.

Funding: CytoX Therapeutics, South San Francisco, CA, USA.

Disclosure: M. Middleton: Grants: Roche, AstraZeneca, GSK. Advisory board: Amgen, Novartis, Rigontec, CytoX. Personal fees: Amgen, Roche, GSK, Novartis, Bristol-Myers Squibb, Eisai, Merck, CytoX-A. Yang Weaver, M: Will; Employee of CytoX Therapeutics. J. Harding: Consultant to Bristol-Myers Squibb. All other authors have declared no conflicts of interest.
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monotherapy in PD-L1–responsive tumor types. Patient recruitment was initiated on January 11, 2017. Key inclusion criteria are: Parts A and B1—advanced, refractory solid tumor or lymphoma in checkpoint inhibitor-naive patients for whom approved PD agents are not available. Part B2—advanced, refractory melanoma with measurable disease that progressed on previous treatment with a PD-1/PD-L1 inhibitor but patients did not discontinue due to toxicity; Part C—checkpoint inhibitor, BRAF-inhibitor, and MEK-inhibitor-naive metastatic V600E BRAF-mutated melanoma. Efficacy will be determined according to RECIST v1.1 criteria, and safety and tolerability will be assessed based on the incidence and nature of dose-limiting toxicities, adverse events (AEs), and serious AEs. Exploratory biomarkers will be used to characterize tumor protease activity, immune response pattern within the tumor, and CX-072 activation in tumor vs peripheral blood.

Clinical trial identification: NCT03013491
Legality entity responsible for the study: CytoXm Therapeutics, South San Francisco, CA, USA
Funding: CytoXm Therapeutics, South San Francisco, CA, USA

Disclosure: J. Wydmanski: Consultant to Bristol-Myers Squibb. B. Irving: Mill: Employee of CytoXm Therapeutics. F. Thistlethwaite: Personal fees from Novartis, Bristol-Myers Squibb, Pfizer, and Ipsen. All other authors have declared no conflicts of interest.

424TIP
Phase 1b multi-indication study of the antibody drug conjugate anetumab ravtansine in patients with mesothelin-expressing advanced or recurrent malignancies

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Background: Mesothelin is expressed in a wide variety of tumours, including mesothelioma, ovarian, pancreatic, gastric/GEJ, NSCLC, triple-negative breast cancer, colorectal cancer, and thymic carcinomas. Anetumab ravtansine (BAY 94-9343), is a novel fully human anti-mesothelin IgG1 antibody conjugated to the maytansinoid tubulin inhibitor DM4 and has shown encouraging anti-tumor activity in mesothelioma and ovarian cancer patients in a phase I study. We will therefore conduct a signal generating study with anetumab ravtansine in six additional high unmet medical need malignancies with mesothelin expression (NCT03013230).

Trial design: Eligibility criteria include: ≥18 years, unresectable locally advanced or metastatic recurrent or relapsing disease, one or more prior lines of therapy, and availability of tumour tissue for mesothelin expression testing. Mesothelin-positive patients with selected adenocarcinomas (NSCLC, triple-negative breast, gastric including gastroesophageal junction) and thymic carcinoma will receive anetumab ravtansine as monotherapy at 6.5 mg/kg IV on a 21-day cycle. Patients with cholangiocarcinoma will receive anetumab ravtansine in combination with cisplatin (25 mg/m2 IV day 1 and 8 on a 21-day cycle for up to 6 cycles) and patients with pancreatic adenocarcinoma will receive anetumab ravtansine in combination with gemcitabine (1000 mg/m2 IV day 1 and 8 on a 21-day cycle). A safety run-in phase (18-24 patients each) will be conducted for the combination regimen prior to enrolling patients in the main study phase. The primary objective of the main phase of the study is objective response rate (ORR) of anetumab ravtansine as monotherapy or combination therapy in patients with either of two mesothelin expression levels ≥30% positive tumour cells with moderate and stronger membrane staining intensity) and low-mid (≥5% all intensities and ≤50% positive tumour cells with moderate and stronger membrane staining intensity). Secondary objectives include safety, disease control rate, duration of response, durable response rate, and progression-free survival. Approximately 348 patients will be enrolled.

Clinical trial identification: NCT03013230
Legality entity responsible for the study: Bayer AG
Funding: Bayer AG

Disclosure: A. Walter: Employee of Bayer AG. L. Cupit, J. Siegel, A. Holynskyj, B.H. Childs, C. Elbi: Employee of Bayer HealthCare Pharmaceuticals Inc. All other authors have declared no conflicts of interest.

425TIP
A phase 1 study of SY-1365, a selective CDK7 inhibitor, in adult patients with advanced solid tumors

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1Medical Oncology, SY-1365-101. ClinicalTrials.gov identifier: NCT03134638.

Legal entity responsible for the study: Syros Pharmaceuticals, Inc.
Funding: Syros Pharmaceuticals, Inc

Disclosure: A. Tolcher: Co-owner of South Texas Accelerated Research Therapeutics which receives fees for consulting and board memberships from companies (17); and research funding from companies (34) for his role as principal investigator. J. Guzman: Employee and stock owner of Syros Pharmaceuticals. N. Waters, D.A. Roth, K. Stephens: An employee and stock holder of Syros Pharmaceuticals. G. Shapiro: Advisory boards for Pfizer, Lilly, G1 Therapeutics, Roche and Vertex Pharmaceuticals. Research funding from Pfizer and Lilly for CDK4/6 inhibitor based projects. All other authors have declared no conflicts of interest.

426TIP
First-in-human study of AMC303 as monotherapy in patients with advanced solid tumor of epithelial origin

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Background: CD44v6 is an isoform of the CD44 family of transmembrane glycoproteins for hyaluronan. High CD44v6 expression was correlated with tumor invasion, metastasis, recurrence and chemoresistance. CD44v6 is a co-receptor of the receptor tyrosine kinase c-Met, RON and VEGFR-2 and it plays a critical role in the development and progression of many types of cancer. Inhibition of CD44v6 efficiently blocks activation of c-Met, RON and VEGFR-2 and intracellular downstream signaling processes. AMC303 is a highly specific and selective inhibitor of CD44v6, which strongly anti-tumor activity was demonstrated in vitro and in vivo. In xenotransplantation animal models, intermittent application of AMC303 resulted in a marked reduction of the primary tumor, prevention of metastatic spread and regression of existing metastases. Good safety and tolerability were demonstrated in pre-clinical studies. The starting dose of 0.1 mg/kg and dose escalation steps are based on the safety profile and are supported by modeling of human pharmacokinetic (PK) profiles from animal exposure studies. Bloching of CD44v6 by AMC303 represents a novel and promising approach to block cancer related RTK pathways by an extracellular acting drug.

Trial design: A First-in-Human Phase I/IIb study in cancer patients was initiated (NCT03099214). The study was designed as a two part open-label, non-randomized, multicentre, dose escalation study with a 3 + 3 design (Part 1) and an expansion cohort at the Maximum Tolerated Dose (MTD)/Recommended Phase 2 Dose (RP2D) (Part 2). Inclusion and exclusion criteria are: Type of cancer (e.g. epithelial cancer for which CD44v6 is known to be highly expressed); ECOG status 0-2, and adequate hematological, renal and hepatic function. Cancer patients are enrolled after failure of conventional therapy or for whom no standard treatment is available. The primary endpoints in Part 1 are safety and tolerability and PK properties. The effects of AMC303 on RTK pathways are analysed in plasma samples (ELISA and Luminex) and mandatory tumor biopsies (immunohistochemistry, protein profiling). Part 2 will focus on selected tumor types as evaluated from the pharmacological effects of AMC303 in part 1.

Clinical trial identification: EuDraCT number: 2016-001358-16
Legal entity responsible for the study: Amcure GmbH
Funding: None

Disclosure: H. Bender, K. Dembrowsky: Employee by amcure GmbH and stock holder. All other authors have declared no conflicts of interest.
Background: Among patients (pts) with advanced carcinoid/neuroendocrine tumors (NETs), expression of PD-L1 is associated with higher tumor grade. The multi-center phase II KEYNOTE-028 study (NCT02054806) evaluated safety and efficacy of pembrolizumab in pts with PD-L1-positive advanced solid tumors. This is the first report from the carcinoid and pancreatic NET (pNET) cohorts of this study.

Methods: Eligibility criteria included: Carcinoid tumors or well- or moderately differentiated pNETs; PD-L1-positive (≥1% modified proportion score or interface pattern, QualTek HIC); failure of standard therapy; and ECOG PS ≤2. Response was assessed every 8 wk for 6 mo then every 12 wk.

Results: 276 screened pts had tumor samples evaluable for PD-L1; 36% were positive. Among enrolled carcinoid (n = 25; lung, n = 9; gut, n = 7; other, n = 9) and pNET (n = 16) pts, respectively, median ages were 63 and 61 y, 76% and 38% had ECOG PS of 1, and 44% and 50% had ≥2 prior therapies for metastatic disease. As of Jan 10, 2017, median (range) follow up was 18.9 (2.0–33.3) and 20.1 (4.5–30.4) mo.

Treatment-related AEs (TRAEs) occurred in 17 (68%) carcinoid and 11 (69%) pNET pts; the most frequent (≥20%) were diarrhea (n = 7, 28%) and fatigue (n = 5, 20%) in carcinoid pts and fatigue (n = 6, 38%) and diarrhea (n = 4, 25%) in pNET pts. Grade ≥3 TRAEs occurred in 8 (32%) carcinoid pts (including diarrhea, n = 3; AST increased, n = 2; ALT increased, n = 2) and 0 pNET pts. One grade 4 AE (increased gamma-glutamyltransferase) and 1 death (unspecified cause) occurred in the carcinoid cohort; neither was treatment related. Three carcinoid pts (12%; 95% CI, 3%–31%) and 1 pNET pt (6%; 95% CI, 3%–30%) had objective responses; SD rates were 60% (n = 15) and 88% (n = 14). Durations of response were 6.9, 9.2, and 11.1 mo for the carcinoid responders; the pNET responder had an ongoing response of 17.6 mo. Conclusion: In pts with heavily pretreated carcinoid/pNET tumors, pembrolizumab was generally well tolerated and, in some pts, provided clinically meaningful antitumor activity.

Clinical trial identification: ClinicalTrials.gov, NCT02054806; EudraCT Number, 2013-004579-37

Legal entity responsible for the study: Merck & Co., Inc., Kenilworth, NJ, USA

Funding: This research was supported by Merck & Co., Inc., Kenilworth, NJ, USA

Disclosure: H.S. Rugo: Research funding: Genentech/Roche, Novartis, Lilly, Eisai, Merck, Pfizer, OBI, Macrogenics, CTX pharma, Travel expenses, including accommodations: Mylan, Puma, B.H. O’Neil: Travel expenses, including accommodations: MSD, AstraZeneca, Novartis, Pfizer. Travel expenses, including accommodations: Merck, BMS, AstraZeneca, Novartis, Pfizer. Travel expenses, including accommodations: Merck, Pfizer, OBI, Macrogenics, CTX pharma. J.C. Soria: Honoraria: MSD. K. Tamura: Direct research support to the responsible project lead (e.g., Principal Investigator): Daichi Sankyo, MSD, Pfizer, AstraZeneca. M. Gould, G. Zhao: Employee of Merck & Co. & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. K. Stein: Employee of Merck & Co. & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. Stock ownership: Merck, Novartis, Sanofi, Pfizer. Travel expenses, including accommodations: Merck. All other authors have declared no conflicts of interest.

Immune landscape of pancreatic neuroendocrine tumours (PanNETs)

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Background: To date little is known about the immune landscape of PanNETs and if immunotherapy could play a role in their treatment. We previously identified 3 molecular subtypes in PanNETs: Metastases-like primary (MLP), intermediate and insulinoma like tumours (PanNETassigner signature, Sadanandam Cancer Discovery 2015).

Here we sought to profile the immune architecture of 48 PanNET patient samples across these subtypes.

Methods: Patients were recruited by the ARC-Net Research Centre Verona, within an ethically approved protocol. Quality RNA was isolated from fresh frozen samples for immune profiling using microarrays, nCounter platform (NanoString Technology) and RNAseq (Illumina). CIBERSORT analysis was performed to assess immune cell enrichment.

Results: 48 PanNET samples were classified using the PanNETassigner gene signature. Based on immune expression profile analysis, tumours were divided into two categories, immune high or immune dormant. The majority of the MLP subtype were immune high, whereas most of the insulinoma and intermediate samples were immune dormant. A small number of insulinoma samples were immune high reflecting the heterogeneity of this tumour. Within the MLP subtype there was increased expression of CD8B, LAG3, CD38, CXCL10, CXCL9, CCL19, CD28 and CD72 compared to the other subtypes. Some of these genes are associated with chronic infection (CD38, CXCL10) whilst others are markers of T cell exhaustion (LAG3). This pattern is consistent with CIBERSORT analysis conducted using microarray data on an overlapping cohort of PanNET samples, where the MLP subtype was associated with increased levels of infiltrating T cells but also an increase in exhausted CD8+ T cells. PDX was highly expressed in 2/5 MLPs. PD1 expression was heterogeneous in MLP but high in 7/13 insulinomas. FOXP3 was highly expressed in a subset of the MLP samples (7/16).

Conclusions: We have demonstrated the differential expression of immune related genes across 3 known PanNET subtypes. The MLP subtype appears to be associated with an immune profile similar to that seen in chronic infection with increased T-cell exhaustion. Such detailed profiling is essential to inform patient selection approaches for further immunotherapy and rational immunotherapy combinations for panNETs in the future.

Legal entity responsible for the study: Institute of Cancer Research

Funding: NIHR Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London

Disclosure: All authors have declared no conflicts of interest.

A phase II trial of palbociclib in metastatic grade 1/2 pancreatic neuroendocrine tumours: The PALBONET study on behalf of the Spanish Taskforce Group of Neuroendocrine Tumors (GETNE)

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Background: Overexpression or amplification of cell cycle regulators like cyclin-dependent kinase 4 (CDK-4), phospho-BH1, or cyclin D1 are observed in 38%, 68%, and 68% pancreatic neuroendocrine tumours (pNETs), respectively. Moreover, these alterations correlate with a more aggressive behavior. Palbociclib targets CDK-4/6 and has shown in vitro activity in pNETs cells overexpressing CDK-4.

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Methods: In this non-randomized, open-label, phase II study, patients (pts) with metastatic grade (G) 1/2 NETs were recruited from 10 centres belonging to the Spanish Taskforce Group of NETS (GETNE). Palbociclib 125 mg was given once daily for 21 of every 28 days until disease progression (DP) or unacceptable toxicity. The initial planned recruitment was 21 patients based on a 2-stage Simon’s phase II design, where palbociclib would be considered ineffective if < 5% of patients achieved an objective response rate (ORR) by RECIST criteria. Type I error rate was 0.05 and the design had 85% power to reject null hypothesis when the true ORR was 5%.

Results: 21 pts were included. One pt withdrew from the study due to clinical deterioration after < 1 month (m). 54% were males, mean age was 54 years (range: 33-66), and 67% had received > 3 previous lines of therapy (23.8% paclitaxel; 80.9% sunitinib; 47.6% erlotinib) beside somatostatin analogs. 20 pts were evaluable for ORR with a median follow up of 10 m (4.2-13.4). No responses (0%) were observed; 11 (55%) pts had stable disease and 6 of them lasted more than 6 m; 7 (33%) pts had progression as best response. 1 pt had tumor shrinkage of 8%. Median PFS was 1.9 m (IC95% 0 - 13). Median OS was 16.6 m (IC95% 9.3 - 23.9). Most frequent toxicities of any grade were anemia (16.2%), diarrhea (6.4%), abdominal pain (4.7%); nausea (4.5%) and neuropathy (4.3%) associated with G3-4 neutropenia (1 case of febrile neutropenia) and 2 pts G3-4 thrombocytopenia.

Conclusions: Lack of activity was observed with palbociclib in 21 molecularly unselected and heavily pretreated patients with advanced G1/2 pNETs. Translational studies correlating activity with molecular tumor markers and Ki67 proliferation index are ongoing.

Clinical trial identification: EudraCT: 2014-003924-34

Legal entity responsible for the study: GETNE (Spanish Taskforce Group for Neuroendocrine Tumors)

Funding: Pfizer

Disclosure: E. Grande Pulido: Advisor for Ipsen, Pfizer, Lexicon. Scientific lecturers for Pfizer and Ipsen. All other authors have declared no conflicts of interest.

4310

Genomic subtypes of pulmonary large cell neuroendocrine carcinoma (LCNEC) may predict chemotherapeutic outcome


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Background: Whether to treat LCNEC with non-small cell lung carcinoma type chemotherapy (NSCLC, i.e. platinum-gemcitabine/taxanes or pemetrexed) or small cell lung carcinoma type (SCLC, i.e. platinum-etoposide) is subject of debate. Recent molecular studies have identified two mutually exclusive genomic LCNEC subtypes, the co-mutated TP53 and RB1 (i.e. SCLC like) and the STK11/KEAP1 (predominantly RB1 wild-type, i.e. NSCLC like) subtype. We determined if genomic LCNEC subtypes are clinically relevant for chemotherapy (CT) outcome.

Methods: Clinical data and tumour specimens were retrospectively obtained from the Netherlands Cancer Registry and Pathology Registry (PALGA, 2003-2012). All first-line CT treated patients with panel-consensus diagnosed LCNEC were included for next-generation sequencing (NGS) analysis for TP53, RB1, STK11, and KEAP1 genes. Furthermore, immunohistochemistry for RB1 (pRB1, 1A10) was analysed (H-score, ≥ 50 considered as positive). NGS and pRB1 results were correlated with overall survival (OS) and progression free survival (PFS) by Kaplan Meier plots and Log-rank test.

Results: LCNEC was panel-consensus diagnosed in 148/232 patients; 79 passed quality control for NGS and 109 for pRB1. RB1 mutations were found in 47% (n = 37) and loss of pRB1 expression in 72% (n = 79) of the cases. Mutations in RB1 were mutually exclusive with mutations in STK11 (n = 8, P = 0.086). Due to reported resistance in neuroendocrine carcinomas, we analysed NSCLC-CT without pemetrexed-CT; OS was significantly longer for NSCLC-CT (n = 15, 9.6 [7.7-11.6] months) compared to SCLC-CT (n = 13, 5.8 [3.5-6.1] months, P = 0.026). LCNEC tumours expressing pRB1 also had longer OS when treated with NSCLC-CT (n = 14, 9.6 [7.4-11.8] m vs. n = 9, 1.9 [1.7-2.1] months, P = 0.001). PFS of RB1 wild-type NSCLC-CT treated patients was significantly longer than SCLC-CT (P = 0.018) also for pRB1 (P = 0.022). In patients with a RB1 mutation OS and PFS were not significantly different for NSCLC-CT vs. SCLC-CT.

Conclusions: In LCNEC with RB1 wild-type, NSCLC-CT correlates with a more favourable outcome compared to SCLC-CT. However, RB1 mutated LCNEC treated with NSCLC-CT have similar clinical outcomes as compared to SCLC-CT. Prospective studies should be initiated.

Legal entity responsible for the study: Maastricht University Medical Center

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Disclosure: H.J.M. Groen: Other from Lily, OSEK, Merck, Pfizer, Roche, BMS, outside the submitted work. E-I. Speet: Other from Pfizer, Roche, Angen, outside the submitted work. A-M. Dingemans: Personal fees from Roche, BMS, Boehringer Ingelheim, AstraZeneca, Eli Lilly, MSD, Pfizer and Asten, outside the submitted work. All other authors have declared no conflicts of interest.

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Prognostic impact of RNA expression profile (EP) in the phase II DECISION trial for patients with advanced radioactive-iodine refractory differentiated thyroid cancer (DTC)

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Background: Neuroendocrine neoplasms (NENs) are a heterogeneous group of tumors with different prognosis. Clinical and pathological factors are used to predict outcome but there are some patients that have a poor outcome even with good clinical prognostic factors. We aimed to define a different RNA expression profile (EP) that could detect patients with worse prognosis and identify possible targetable new pathways.

Methods: We identified 48 paraffin-embedded archival tumor material of patients with metastatic grade 1/2 NENs of small intestine origin for RNAsequencing. We generated on average 66 million paired-end reads for each sample on HiSeq2500 (Illumina). RNAseq reads were mapped against the human reference genome (hg19) with TopHat (v2.0.14) and quantified using Cufflinks tools suite (v.2.2.1). 41 samples had sufficient quality to be included in the analysis. We used multivariate Cox proportional models to study the association between EP, clinical variables (gender, age, location of metastases, hormone production and Ki67 index) and overall survival (OS). We defined as poor outcome those patients that died within the first 3 years of the diagnosis of advanced disease.

Results: 9348 transcripts were quantified. A gene signature of 329 transcripts was defined by a two-way statistical analysis between poor and long term survivors. A pathway enrichment analysis of these genes showed a deregulation in the poor prognosis group on the PI3K/Akt-mTOR and the Toll-like receptor signaling pathways. The hazard ratio (HR) for mOS defined by EP comparing poor and long term survivor groups was 0.33, 95% CI 0.1-1.1, P = 0.081 in the univariate analysis and HR of 0.05, 95% CI 0.005-0.51, P = 0.011 in the multivariate analysis.

Conclusions: We identified statistically different RNA-clusters and different deregulated pathways for those patients with advanced NENs of small intestine origin with poor prognosis. To our knowledge, this is the first time that Toll-like pathway is involved in the pathogenesis of NENs. These results are relevant as they may help improve the prognosis stratification of patients and involve novel targetable pathways of great clinical potential.

Legal entity responsible for the study: Vall d’Hebron Institute of Oncology

Funding: Spanish Task Force for Neuroendocrine and Endocrine Tumors (GETNE)

Disclosure: All authors have declared no conflicts of interest.

4320P

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interest.

Conclusions: RNA-seq analysis identifies 3 different expression profiles in DTC: BRAF-like, RAS-like and non-BRAF/RAS-like. BRAF-like EP includes almost all BRAF mutant tumors but also a 45% of tumors with no mutation in BRAF gene. In the multivariate analysis, BRAF-like EP has shown a better prognostic factor for PFS in DTC and biomarkers (EP and MS) with PFS and OS.

Results: The clinical variables in each expression profiles are shown in Table. Multivariable analysis indicated that only sorafenib treatment (HR: 0.39, 95% CI 0.23-0.66, p < 0.001), age (HR: 0.97, 95% CI 0.94-0.99, p = 0.002) and BRAF-like EP (HR = 0.41, 95% CI 0.17-0.99, p = 0.046) were independent prognostic factors for PFS. No significant prognostic factors were identified for OS. However, in papillary histology (PTC), only the BRAF-like EP was associated with outcome (HR = 0.52, 95% CI 0.18-1.18, p = 0.046) were independent prognostic factors for PFS.

Conclusions: RNA-seq analysis identifies 3 different expression profiles in DTC: BRAF-like, RAS-like and non-BRAF/RAS-like. BRAF-like EP includes almost all BRAF mutant tumors but also a 45% of tumors with no mutation in BRAF gene. In the multivariate analysis, BRAF-like EP has shown a better prognostic factor for PFS in DTC and biomarkers (EP and MS) with PFS and OS.

Legal entity responsible for the study: Vall d’Hebron Institute of Oncology

Funding: Bayer HealthCare Pharmaceuticals, Inc.

Conflict of interest: C. Peña: Bayer employee. All other authors have declared no conflicts of interest.

<table>
<thead>
<tr>
<th>Table: 432PD Clinical variables in each expression profiles</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRAF like (n = 56)</strong></td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
</tr>
<tr>
<td><strong>ECOG</strong></td>
</tr>
<tr>
<td><strong>Tumor histology</strong></td>
</tr>
<tr>
<td><strong>BRAF status</strong></td>
</tr>
<tr>
<td><strong>RAS status</strong></td>
</tr>
</tbody>
</table>

Table: 433PD

<table>
<thead>
<tr>
<th>PTC</th>
<th>FTC</th>
<th>MTC</th>
<th>ATC</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Patients</td>
<td>408</td>
<td>77</td>
<td>113</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>59</td>
<td>60</td>
<td>54</td>
</tr>
<tr>
<td>Gender (F/M)</td>
<td>215/193</td>
<td>37/40</td>
<td>46/67</td>
</tr>
<tr>
<td>GA/tumor</td>
<td>2.75</td>
<td>3.01</td>
<td>1.96</td>
</tr>
<tr>
<td>Significant genes altered</td>
<td>BRAF TERT TP53 RET</td>
<td>TERT NRAS TP53 PTEN HRAS</td>
<td>RET VHL MEN1</td>
</tr>
<tr>
<td>TP53 GA Frequency</td>
<td>11%</td>
<td>16%</td>
<td>2%</td>
</tr>
<tr>
<td>RET GA Frequency</td>
<td>9%</td>
<td>0%</td>
<td>81%</td>
</tr>
<tr>
<td>hTERT Frequency</td>
<td>58%</td>
<td>67%</td>
<td>1%</td>
</tr>
<tr>
<td>BRAF GA Frequency</td>
<td>73%</td>
<td>7%</td>
<td>0%</td>
</tr>
<tr>
<td>BRAF, RET, ALK, or NTRK rearrangements</td>
<td>13%</td>
<td>0%</td>
<td>3%</td>
</tr>
<tr>
<td>Total Mutational Burden ≥10 mut/Mb</td>
<td>2%</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Opportunity for Targeted Therapies</td>
<td>High (BRAF, oncogenic fusions)</td>
<td>Low (RET)</td>
<td>Moderate (BRAF, oncogenic fusions)</td>
</tr>
</tbody>
</table>
4 mTC tumor types with only 3 mTC (<1%) having ≥ 20 mu/Mb. Examples of mTC with responses to targeted therapies will be presented.

Conclusions: Refractory mTC patients are generally older than patients with classic localized primary PTC, and feature relatively more males. Advanced stage PTC, and to a lesser extent ATC, is frequently driven by BRAF G61 or oncocentric rearrangements. Relapsed MTC is nearly universally driven by RET/TA, whereas FTC has no dominant driver GA identified. TMB appears to be low for all subtypes of MTC, suggesting low potential for immunotherapy.

Legal entity responsible for the study: Jeffery S. Ross

Funding: None


434PD Impact of duration of dose interruption on the efficacy of lenvatinib (LEN) in a phase 3 study in patients (pts) with radioiodine differentiated thyroid cancer (RR-DTC)

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Background: LEN prolonged progression-free survival (PFS) in pts with RR-DTC in the SELECT trial, and efficacy was maintained in all subgroups. Toxicity was manageable with dose modifications, but whether a longer period of dose interruption might impact the efficacy of LEN was unclear.

Methods: In SELECT, pts were randomized 2:1 to receive LEN 24 mg/day or placebo. Pts assigned to LEN were divided into 2 groups: pts with duration of dose interruption <10% (A) and pts with duration of dose interruption ≥10% (B) of total treatment duration. A and B were not randomized groups. PFS, objective response rate (ORR), and safety were analyzed in both groups.

Results: Of 261 LEN-treated pts, there were 134 in group A and 127 in group B. Differences in pt characteristics between groups (A and B) were, respectively: age (>65 years, 33% and 49%), race (Asian, 10% and 25%), and ECOG performance status (0, 64% and 46%). Median duration of dose interruption was 19 days (range: 0–63) and 61 days (range: 2–266) in groups A and B, respectively. Median PFS was not reached (hazard ratio [HR] to placebo: 0.14, 95% CI: 0.09-0.20, P < 0.001) in group A and 12.8 months (HR to placebo: 0.31, 95% CI: 0.22–0.43) in group B. ORR was 76% for group A and 53% for B. Disease control rate was 88% and 87% in groups A and B, respectively. Common adverse events (AEs) in both groups were diarrhea (A: 24%; B: 21%), hypertension (A: 16%; B: 24%), proteinuria (A: 23%; B: 42%). Common AEs leading to dose interruption or reduction were diarrhea (A: 10%; B: 27%), weight (A: 57%; B: 44%), palmar-plantar erythrodysesthesia (A: 27%; B: 38%), and anemia (A: 11%; B: 26%). Common AEs leading to dose interruption were rash (A: 24%; B: 21%), hypertension (A: 16%; B: 24%), proteinuria (A: 11%; B: 26%), and decreased appetite (A: 10%; B: 27%).

Conclusions: Longer duration of dose interruption may negatively affect the potential efficacy of LEN. Management of toxicities is essential to avoid long dose interruption. Differences in pt characteristics might confound the results. However, in this analysis LEN achieved improved PFS and ORR compared to placebo, regardless of length of dose interruption.

Clinical trial identification: NCT01321554

Legal entity responsible for the study: Eisai Inc

Funding: Eisai Inc

Disclosure: M. Tahara: Grants and personal fees from Eisai during the conduct of the study and personal fees from Merck Serono, BMS, and Bayer outside the submitted work. M.S. Brose: Grants from Eisai during the conduct of the study. Grants and personal fees from Bayer HealthCare Pharmaceuticals, Exelixis, and Onyx. Grants from Novartis and Roche/Genentech outside the submitted work. L. Wirth: Personal fees from Eisai and Novartis outside the submitted work. T. Suzuki, K. Fujino: Employee of Eisai Co., Ltd. N. Batty, C. Dutcsu: Employee of Eisai Inc. A. Gianoukakis: Grants and nonfinancial support from Eisai during the conduct of the study.

434PD Preliminary safety and efficacy of rovalpituzumab tesirine in patients with delta-like protein 3-expressing advanced solid tumors

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Background: Delta-like protein 3 (DLL3) is an a NTch receptor family ligand expressed in high-grade neuroendocrine carcinomas (NECs), but not in normal tissue. Rovalpituzumab tesirine (Rova-T) is an antibody-drug conjugate targeting DLL3. A Phase 1 study of Rova-T in small cell lung cancer showed encouraging antitumor activity in patients (pts) with DLL3 expression, and was well-tolerated1. Rova-T may also be active in other DLL3-expressing tumors.

Methods: This is a Phase 1/2, open-label, multicenter study (NCT02798889) to determine safety and tolerability of Rova-T in 8 cohorts: malignant melanoma, medullary thyroid cancer (MTC), glioblastoma (GBM), large cell NEC (LCNEC), neuroendocrine prostate cancer (NEPC), high-grade gastroenteropancreatic NEC (GEP NEC), other NEC and other solid tumors. Eligible adults have a histologically confirmed, DLL3-expressing, advanced solid tumor relapsed/refractory to standard therapy, and no prior exposure to a pyrobenzodiazepine-based drug. A 3 + 3 dose escalation is used in each cohort, at doses 0.2–0.4 mg/kg. A total of 11 dose levels were planned, with 1 of each 42-day cycle, and proceeding until a maximum tolerated dose (MTD) is determined. A 2-stage design will be used for disease-specific expansion cohorts.

Results: As of 3 April 2017, 31 pts (2 melanoma, 2 MTC, 3 GBM, 3 LCNEC, 3 NEPC, 3 GEP NEC, 10 other NEC, 5 other solid tumor) have been treated (26 pts at 0.2 mg/kg, 5 pts at 0.3 mg/kg Rova-T). The MTD has not been reached. Twenty-six pts (84%) had an adverse event (AE), and only 3/31 pts (10%) had a Grade 3+ AE deemed to be related to Rova-T. Common AEs were fatigue (32%), nausea (29%), and constipation (23%). Four pts had serosal effusions, 2 (6%) of which were assessed to be drug-related, and 3 pts (10%) had adverse skin reactions. Ten pts (32%) discontinued treatment, 5 for progressive disease and 4 due to AEs. Eleven pts had post-baseline tumor assessments, and anti-tumor activity has been observed in multiple disease cohorts.

Conclusions: Preliminary safety and efficacy data of Rova-T warrant continued study in these disease populations, and will be updated at time of presentation.


Clinical trial identification: NCT02798889

Legal entity responsible for the study: AbbVie Stemmctn

Funding: AbbVie Stemmctn

Disclosure: A. Mansfield: Consulting to Genentech, BMS and Trovare with honorsoria provided to institution, H. Beltran, K. Lewis: Research funding from AbbVie Stemmctn LLC, A.F. Farago: Consulting or advisory role for AbbVie, Pharmamar, Merrimack Pharmaceuticals, Takeda, Intervention Insights, Honorarium from Foundation Medicine, C.L. Hann: Advisory board for AbbVie Stemmctn and BMS, Research funding from GlaxoSmithKline and Merrimack Pharmaceuticals. S. Richey: Employee of Texas Oncology Consulting or advisory role for Exelixis, Pfizer, Prometheus and Sanofi. Research funding from Novartis, BMS, Exai, Genentech/ Roche, GSK, and AbbVie. D. Smith: Research funding from US Oncology. H.P. Soares: Advisory board for Cornerstone Pharmaceuticals. Research funding from Novartis. Consultant fees/honoria for Ipsen. A. Spira: Consultant for AbbVie. Research funding from AbbVie (to institution). S. Lally, M. Rossi, L. Saunders, S.J. Dyda, E. Kavalerchik: Employee of AbbVie Stemmctn and may own stock. L. Anthony: Research funding from AbbVie Stemmctn, Lexicon Pharmaceuticals, Novartis, Markey Cancer Center Foundation. All other authors have declared no conflicts of interest.
Background: Several attempts to improve the knowledge about the molecular biology of EP-NETS have been made. Several studies rely on alterations or pattern description rather than integrative analysis of the findings derived from different platforms. We aimed to identify new potential biomarkers integrating the differential expression of miRNAs and DNA methylated regions.

Methods: From a series of 115 EP-NETS formalin-fixed and paraffin embedded samples, we selected 8 cases of small intestine (SI) NETS and 8 pancreatic (P) NETS based on tumor grade, location of primary tumor, functionality, previous therapies, and the results of somatostatin receptor (SSR) PET/CT was used for restaging and response to therapy assessment (EORTC criteria). Accordingly, overall survival (OS) and progression-free survival (PFS) were calculated. Adverse events (hematotoxicity and nephrotoxicity) were determined by CTCAE (v4.03).

Results: Overall survival (95% CI) was 51 months (47.0-54.9) and differed according to tumor grade, location of primary tumor, functionality, previous therapies, and the results of somatostatin receptor (SSR) PET/CT was used for restaging and response to therapy assessment (EORTC criteria). Accordingly, overall survival (OS) and progression-free survival (PFS) were calculated. Adverse events (hematotoxicity and nephrotoxicity) were determined by CTCAE (v4.03).

Conclusions: This analysis from the NETTER-1 Phase III study demonstrates that 177Lu-DOTATATE provides a significant quality of life benefit for patients with progressive midgut NETs compared to high-dose octreotide. In addition to the meaningful increase in progression-free survival already reported.

Clinical trial identification: NCT01578239

Legal entity responsible for the study: NETTER-1 study group and Advanced Accelerator Applications

Funding: Advanced Accelerator Applications

Disclosure: M. Lopera Sierra: Advanced Accelerator Applications Chief Medical Officer. E. Krenning: Stock ownership. All other authors have declared no conflicts of interest.

439PD

Peptide receptor radionuclide therapy of neuroendocrine neoplasms using lutetium-177 and yttrium-90 labeled somatostatin analogs: A single center experience in over 1000 patients

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Background: Peptide receptor radionuclide therapy (PRRT) of patients with somatostatin receptor expressing gastroenteropancreatic neuroendocrine neoplasms (NEN) has shown promising results in a recently published clinical trial (NETTER-1, NEJM, Jan 2017). In this study, we performed an intention to treat analysis in over 1000 patients with NEN (pancreas, mid-gut, lung and other) treated at our center.

Methods: From 2004, 1048 patients received at least one cycle of Yttrium-90 or Lutetium-177 based PRRT, and were included in an intention to treat analysis. Ga-68 somatostatin receptor (SSR) PET/CT was used for restaging and response to therapy assessment (EORTC criteria). Accordingly, overall survival (OS) and progression-free survival (PFS) were calculated. Adverse events (hematotoxicity and nephrotoxicity) were determined by CTCAE (v4.03).

Results: Overall survival (95% CI) was 51 months (47-54.9) and differed according to tumor grade, location of primary tumor, functionality, previous therapies, and the results of somatostatin receptor (SSR) PET/CT was used for restaging and response to therapy assessment (EORTC criteria). Accordingly, overall survival (OS) and progression-free survival (PFS) were calculated. Adverse events (hematotoxicity and nephrotoxicity) were determined by CTCAE (v4.03).

Conclusions: PRRT is effective as it favors prolong the OS and PFS in patients with metastatic neuroendocrine neoplasms. However, this depends on the tumor grade, location of primary tumor, and the radionuclide used for therapy. Low rate of severe hematotoxicity and nephrotoxicity were observed. There was no therapy associated severe nephrotoxicity in patients with normal renal function prior to commencement of PRRT.

Legal entity responsible for the study: Richard P. Baum

Funding: None

Disclosure: All authors have declared no conflicts of interest.

437PD

Integrative DNA methylome and miRNA transcriptome analysis for new biomarker discovery in entero-pancreatic neuroendocrine tumours (EP-NETS)

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Background: Several attempts to improve the knowledge about the molecular biology of EP-NETS have been made. Several studies rely on alterations or pattern description rather than integrative analysis of the findings derived from different platforms. We aimed to identify new potential biomarkers integrating the differential expression of miRNAs and DNA methylated regions.

Methods: From a series of 115 EP-NETS formalin-fixed and paraffin embedded samples, we selected 8 cases of small intestine (SI) NETS and 8 pancreatic (P) NETS based on tumor grade, location of primary tumor, functionality, previous therapies, and the results of somatostatin receptor (SSR) PET/CT was used for restaging and response to therapy assessment (EORTC criteria). Accordingly, overall survival (OS) and progression-free survival (PFS) were calculated. Adverse events (hematotoxicity and nephrotoxicity) were determined by CTCAE (v4.03).

Results: Overall survival (95% CI) was 51 months (47-54.9) and differed according to tumor grade, location of primary tumor, functionality, previous therapies, and the results of somatostatin receptor (SSR) PET/CT was used for restaging and response to therapy assessment (EORTC criteria). Accordingly, overall survival (OS) and progression-free survival (PFS) were calculated. Adverse events (hematotoxicity and nephrotoxicity) were determined by CTCAE (v4.03).

Conclusions: This analysis from the NETTER-1 Phase III study demonstrates that 177Lu-DOTATATE provides a significant quality of life benefit for patients with progressive midgut NETs compared to high-dose octreotide. In addition to the meaningful increase in progression-free survival already reported.

Clinical trial identification: NCT01578239

Legal entity responsible for the study: NETTER-1 study group and Advanced Accelerator Applications

Funding: Advanced Accelerator Applications

Disclosure: M. Lopera Sierra: Advanced Accelerator Applications Chief Medical Officer. E. Krenning: Stock ownership. All other authors have declared no conflicts of interest.

438PD

Improved time to quality of life deterioration in patients with progressive midgut neuroendocrine tumours treated with 177Lu-DOTATATE: THE NETTER-1 phase III trial


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Background: Neuroendocrine tumor (NET) progression is associated with deterioration in quality of life (QoL). We assessed the impact of 177Lu-DOTATATE treatment on the time to clinically relevant change (deterioration) in health-related QoL (HRQoL). The NETTER-1 trial is an international phase III study in patients with progressive, somatostatin receptor positive midgut NET. Patients were randomized to receive treatment with 177Lu-DOTATATE versus high-dose (60 mg) Octreotide LAR (octreotide). EORTC questionnaires QLQC-30 and G.I.NET-21 were assessed during the trial to determine the impact of treatment on HRQoL.

Methods: 231 patients completed EORTC QLQC-30 and G.I.NET-21 questionnaires at baseline and every 12 weeks thereafter until tumor progression was confirmed. QoL scores were converted to a 100-point scale according to EORTC instructions and individual changes from baseline scores were assessed. Time to QoL deterioration (TTD) was defined as the time from randomization to the first QoL deterioration ≥10 points for each patient in the corresponding domain scale. This magnitude of variation was considered clinically relevant. All analyses were conducted on the ITT population.
Efficacy and safety of telotristat ethyl in patients with carcinoid syndrome inadequately controlled by somatostatin analogs: Analysis of the completed TELESTAR extension period


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Background: The phase III, placebo-controlled, randomized TELESTAR study evaluated efficacy and safety of telotristat ethyl (TE) in patients (pts) with diarrhea (>2 bowel movements [BM]/day) due to carcinoid syndrome (CS) inadequately controlled by somatostatin analogs (SSAs). TE, a tryptophan hydroxylase inhibitor, decreases peripheral serotonin levels. As add-on treatment to SSAs, TE 250 mg 3x/day (tid) and TE 500 mg tid significantly reduced BM frequency (p < 0.001) compared with placebo over the 12-week Double-Blind Treatment (DBT) period. After Week 12, pts crossed over to a 36-week Open-label Extension (OLE) period with TE 500 mg tid, data from the full 48 weeks are presented.

Methods: Changes from baseline in BM frequency (monitored weekly), urinary 5-hydroxyindole acetic acid (U-HIAA), Weeks 18, 24, and 48, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) score (Weeks 24 and 48), and safety during the OLE period were evaluated.

Results: Of the 115 pts randomly assigned, 118 completed the DBT period, 115 pts subsequently entered (and 97 completed) the OLE period. Of the 36 pts who discontinued the OLE period, the most frequent reasons were adverse event (AE; 15 pts) and withdrawal of consent (9 pts). Treatment-emergent AEs led to discontinuation in 10 pts due to gastrointestinal disorder was the most commonly reported reason (6 pts). Reductions from baseline in BM frequency (~2 BMs/day) and U-HIAA levels (~20 mg to ~49.3 mg/24 hours) during the OLE were consistent with results of the DBT period and persisted through Week 48. Improvement in EORTC QLQ-C30 diarrhea subscale scores relative to baseline (range ~18.8 to ~30.6 points) was notable and persisted through Week 48. Crossover into the OLE period was well tolerated. Treatment-emergent AEs were mainly mild to moderate and occurred at a similar rate as in the DBT period.

Conclusions: Patients benefited from TE throughout the OLE period. TE was well tolerated over 48 weeks and its efficacy was consistent with previously reported data.

Clinical trial identification: NCT01677910

Legal entity responsible for the study: Lexicon Pharmaceuticals, Inc.

Funding: Lexicon Pharmaceuticals, Inc.


Follow-up recommendations for completely resected gastroenteropancreatic neuroendocrine tumours (GEP-NETs): Consensus guidelines from the Commonwealth NET collaboration (CommNETs) in conjunction with the North American NET Society (NANETS)


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Background: NETs are uncommon, and there is no consensus regarding the optimal follow-up frequency or modality after resection. Current follow-up guidelines for resected GEP-NETs are based on limited evidence and our large, international practice survey showed poor compliance by NET expert clinicians. A need for clear and practical guidelines was identified.

Methods: A RAND/UCLA appropriateness process was employed given the lack of published data. A systematic review was undertaken as well as a multi-national practice survey to understand current follow-up patterns. Results from two large retrospective reviews (Ontario, Canada and Tampa, Florida) examining outcome following curative surgery were obtained. An 18-member multidisciplinary international panel scored 193 clinical scenarios for appropriateness of timing of consultations and investigations for detecting recurrence on a 1-9 scale. At a face-to-face consensus conference, the final follow-up recommendations were developed.

Results: Twelve studies were identified describing follow-up strategies post-resection, with only one comparing follow-up strategies. Data from our practice survey (n = 163) and our population-based study (n = 990) are separately reported. Based on the scenarios, panel scored 14 summary statements, with the major themes of (1) less frequent follow-up visits and investigations within the first five years (2) follow-up even beyond 10 years (3) different recommendations for pancreatic versus gastrointestinal NETs (4) identification of low risk subgroups where no routine follow-up was recommended (5) no role for any serum or urine biomarkers, or chest imaging (6) the need to evaluate functional imaging in follow-up.

Conclusions: Streamlined, practical guidelines were developed for the follow-up of patients with resected GEP-NETs. These guidelines differ significantly from other current guidelines. The expert consensus was informed by previously unavailable large outcomes datasets. Compliance, cost-effectiveness and patient acceptability will be evaluated in future studies.

Legal entity responsible for the study: Sunnybrook Research Institute

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Follow-up recommendations for completely resected gastroenteropancreatic neuroendocrine tumours (GEP-NETs): Consensus guidelines from the Commonwealth NET collaboration (CommNETs) in conjunction with the North American NET Society (NANETS)
Results: A total of 239 patients with CS received treatment with TE in Phase 2 and 3 clinical trials. For these patients, as of the end of 2016, the mean duration of exposure was 1.3 years, and maximum 5.7 years. The leading causes of hospitalization were gastrointestinal disorders and surgical and medical procedures, mostly attributable to the underlying tumor and related treatment. Survival estimates at 1, 2, and 3 years were 93%, 88%, and 77%, respectively. Nearly all deaths were due to progression or complication of the underlying disease, and none were attributable to TE. There was 1 death in Year 4 and no deaths in Years 5 and 6 of patient follow-up in this data set. The median survival with TE was not reached at the end of the 6-year follow-up period.

Conclusions: Our review of the long-term safety data for TE indicates that patients with CS treated with TE in Phase 2 and 3 studies experienced encouraging survival rates.

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443P Identifying symptom and quality of life improvements in patients with carcinoid syndrome treated with telotristat etyl: Qualitative patient exit interviews from the TELESTAR Trial

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Background: Carcinoid syndrome (CS) is a rare condition in patients (pts) with neuroendocrine tumors (NETs), characterized by diarrhea, flushing, and abdominal pain that impact health-related quality of life (HRQoL). We assessed symptoms and HRQoL in pts with inadequately-controlled CS enrolled in TELESTAR (NCT01677910).

Methods: English or German-speaking pts randomized 1:1:1 to 12 wks of double-blind (DB) treatment with telotristat etyl (TE) 250mg, 500mg, placebo were invited to a blinded, qualitative, semi-structured exit interview after the DB period to assess symptoms, HRQoL concepts (improved/not changed/worsened), and TE treatment effects. Concepts were freely reported by pts and not solicited. EORTC QLQ-C30 and GINET21 questionnaires were reviewed, and daily diaries assessed baseline (BL) bowel movement (BM) frequency.Analyses compared pts with durable response (DRs; predefined as a daily BM frequency reduction of ≥ 30% from BL for ≥ 50% of DB period) and without durable response.

Results: TELESTAR enrolled 135 pts, 45 per group. 34 pts (9, 16, 9 in TE 250mg, 500mg, placebo, respectively), including 10 DRs consented to interviews. BL age, gender, BMI, wk of interviewed pts (IPs) were similar to non-interviewed pts. Most qualitative concepts were captured, to an extent, by the QLQ-C30; most common symptoms, HRQoL concepts identified were daily life activities, physical, and psycho-social. The most common symptoms (improvement/no change) reported in all IPs were diarrhea consistency (n = 17/n = 10), frequency (n = 17/n = 9), urgency (n = 17/n = 7), flushing (n = 11/n = 7), and fatigue (n = 9/n = 4). A higher proportion of TE-treated pts and DRs reported symptom and HRQoL concept improvements. Durable response (p < 0.001) and treatment satisfaction (p = 0.0137) correlated with diarrhea QLQ-C30, but no other QLQ-C30/GINET21 scores.

Conclusions: The QLQ-C30 covered most qualitative concepts, but due to the lack of emphasis on key symptoms, may not adequately reflect pt perspectives. Interviews suggested improvements in symptoms and HRQoL with TE treatment and in DRs.

Clinical trial identification: NCT01677910

Legal entity responsible for the study: Lexicon Pharmaceuticals

Funding: Lexicon Pharmaceuticals and Ipsen Pharma SAS


444P Carcinoid syndrome: Patient outcomes from a European Neuroendocrine Tumour Society (ENETS) centre of excellence

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Background: Carcinoid syndrome (CS), characterised by flushing, diarrhea, wheeze and histronic valvulopathy, arises in patients (pts) with advanced NETs due to serotonin and kallikrein secretion.

Methods: Sequential pts with advanced well-differentiated gastroenteropancreatic NETs (GEP-NETs) treated at The Christie (1998-2017) with ≥ 1 carcinoid symptom(s) and raised serum/urinary 5-hydroxyindoleacetic acid (5-HIAA) were identified. Ratio of 5-HIAA/upper limit normal (ULN) was calculated. Progression-free (PFS) and overall survival (OS) were estimated (Kaplan-Meier method) and prognostic factors identified (Cox proportional hazards model).

Results: Of 882 pts, 139 (16%) had CS: median (med) age 64 yrs, 55% male, 80% performance status (PS) 0-1, 13% PS 2; 65% had small bowel primary, 10% large bowel, 4% pancreas, 0.7% gastric, 21% unknown primary (consistent with GEP-NET origin). Tumour grade (G) was 1 in 45%; G2 in 29%: symptoms included diarrhea (91%), flushing (89%), wheeze (22%), and carcinoid heart disease (CHD, 35%). Fifty-seven (41%) had primary resection, and 121 (87%) had liver metastases. In first line, 66% received a somatostatin analogue (SSA), 20% debulking surgery, 14% other. Med baseline 5-HIAA levels were 8.45 x ULN (urinary: 10.56 x ULN, serum: 6.07 x ULN). Med follow-up was up to 47.5 months (mo). Med PFS and OS were 27.0 (95%CI 17.2-35.5) and 65.4 (95%CI 50.4-76.4) mo. In univariate analysis, small bowel primary (P = 0.045), liver metastases (P = 0.03), Ki-67 (P < 0.01) and 5-HIAA baseline ratio (P < 0.001) were prognostic for PFS; and age (P = 0.01), PS (P < 0.01), primary in situ (P < 0.001), CHD (P = 0.03), Ki-67 (P < 0.005), baseline 5-HIAA ratio (P < 0.001) and use of SSA vs surgery (P = 0.02) were prognostic for OS. On multivariable analysis, high Ki-67 (HR 1.06, 95%CI 1.00-1.12, P = 0.049) and baseline 5-HIAA ratio (HR 1.03, 95%CI 1.01-1.05, P = 0.001) were prognostic for worse PFS. Primary in situ (HR 2.23, 95%CI 1.09-4.54, P = 0.03) and high baseline 5-HIAA ratio (HR 1.02, 95%CI 1.00-1.04, P = 0.04) were prognostic for worse OS. Change in 5-HIAA at 6 mo was not prognostic for PFS (P = 0.42) or OS (P = 0.40).

Conclusions: Baseline 5-HIAA ratio, but not change from baseline to 6 months, was prognostic for PFS and OS. Treatment optimisation is pivotal.

Legal entity responsible for the study: Audit Department - The Christie NHS Foundation Trust, Manchester

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functioning (51.1-4.7, 14.9%), nausea/vomiting (-7.5 [-15.4, 0.4]), pain -16.0 [-27.0, -5.0]), dyspepsia -5.7 [-15.5, 4.1]), diarrhea -14.7 [-26.5, -2.9]), and CIN2T2 gastro-intestinal symptoms -9.3 [-16.3, -2.2]) versus NRIs.

Conclusions: Durable response was associated with reductions in the symptoms and overall clinical burden of CS. DIAs showed significant and/or meaningful improvements in global HRQoL, nausea, pain, diarrhea, and gastrointestinal symptoms.

Clinical trial identification: NCT0167910

Legal entity responsible for the study: Lexicon Pharmaceuticals

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446P Benefit of oral monotherapy with pazopanib in metastatic gastroenteropancreatic neuroendocrine tumours

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Background: Although standard therapy for gastroenteropancreatic neuroendocrine tumours (GEP-NETs) can provide symptom relief and delay tumour progression, new strategies are needed for patients with metastatic disease. The aim of this study was to investigate the antitumour activity and safety profile of pazopanib - a selective mult-targeted receptor tyrosine kinase inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor.

Methods: We enrolled 124 patients with metastatic GEP-NETs. Pazopanib was administered orally at a dose of 800 mg daily with a 28-day cycle. The primary endpoint was overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors. The secondary endpoints were overall survival (OS), progression-free survival (PFS) at 6 months and safety profile of pazopanib (general tolerability and toxicity).

The third endpoint was to compare the clinicopathological features of tumours and biomarker analysis with survival of the patients.

Results: The mean follow-up time was 196.87 days with a range of 67-268 days; 26 patients died within the observation time. 69% of the patients had confirmed pancreatic GEP-NET and 53% had colorectal, gastric and duodenal GEP-NET. 59 (47.6%) patients had Gl, 34 (27.4%) G2 and 31 (25%) had G3 GEP-NET. ORR was 24% (19 of 124 patients), stable disease was achieved in 49 patients (39.5%) and PFS at 6 months was 36%. Median OS was 10.2 months (95% CI 5.4-15.2 months). The most common grade 3-4 adverse events attributed to therapy were neutropenia (11%), proteinuria (14%), diarrhea (7%), and fatigue (12%). Patients with high CEA levels had the highest mortality risk (hazard ratio 3.478, 95% confidence interval 1.313-4.727, p < 0.01) and worse outcomes. Furthermore, extremely high CEA levels (≥8000 ng/ml, range 8000-1000 ng/ml) were associated with low survival independently from the Ki-67 score in a multivariate Cox regression model.

Conclusions: Pazopanib demonstrated a comparable therapeutic efficiency as well as a satisfying safety profile compared to other targeted agents in the treatment of patients with metastatic GEP-NETs.

Legal entity responsible for the study: Faculty of Medicine Osijek

Disclosure: All authors have declared no conflicts of interest.

446B Bone metastases in patients with neuroendocrine neoplasms: A survey of natural history and clinical management

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Background: Bone metastases (BM) in neuroendocrine neoplasms (NEN) represent a poorly defined issue.

Methods: This is a nationwide survey among Italian institutions dealing with NEN patients. Characteristics of BM, clinical management, skeletal related events (SREs) and disease outcome were recorded.

Results: We analysed 321 patients with histological diagnosis of NEN and BM collected from 18 Italian Centers. Mean age was 59 y.o. (range 13-86). Primary sites were 47% gastroenteropancreatic (GEP), 36% lung, 4% Paraganglioma/Pheochromocytoma (Par/ Pheo), 7% unknown, 9% others. The vast majority (72%) of NEN were already metastatic at diagnosis and the liver represented the second most frequent site of metastasis (in 77% of patients) during follow-up, in addition to BM. Bone was the first metastatic site in 41% of cases. Neoplasms were low/intermediate grade in 80% and high grade in 20%. SREs occurred in 32% of cases, mainly in lungs and others. Median time to SRE was 4 months. It strictly correlated with the high grade, irrespective of the primary site. Bisphosphonates were administered in 32% of patients. Median survival from BM diagnosis was 65 months (range 45-78) in the whole population, with Par/Pheo at the best and high grade GEP at the worst limit. SRE, high grade (or in alternative high Ki-67) and prior lung metastases resulted significantly associated with worse overall survival at the multivariable analysis. After adjustment for tumor grade, survival of patients with GEP and lung NENs were similar.

Conclusions: This is one of the largest series of NEN patients with BM reported so far. This survey mirrors the Italian real clinical practice in this setting, as it included most Centers involved in NEN patients’ management. It showed that overall, BM from NEN are associated with a relatively long survival. Bisphosphonates were used in a low percentage of cases, probably related to SRE. Tumor grade confirmed its value in separating two survival categories, irrespective of primary site. The results of this analysis generated hypotheses for prospective trials in homogeneous clinical settings.

Legal entity responsible for the study: Nicola Fazio

Disclosure: None

All authors have declared no conflicts of interest.
Financial toxicity in patients with neuroendocrine tumors: Impact of a chronic disease on patients’ economic situation

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Background: The diagnosis of cancer imposes physical, emotional and financial burdens on patients. So far, the socio-economic impact of cancer for patients in Germany is poorly understood. The aim of the project is to provide an overview on patients’ financial losses due to a neuroendocrine tumor (NET) diagnosis as well as possible psycho-social effects.

Methods: This prospective quantitative study recruited n = 123 patients with NET from November 2016 to March 2017 at the National Center for Tumour Diseases, University Hospital Heidelberg. They completed a survey on patients’ income, cancer-related out-of-pocket costs, disease burden (Distress Thermometer), quality of life (EORTC-LQ 29/30), health status (EQ-5D) and demographic data.

Results: 78.0% (n = 96) of the patients stated to have higher out-of-pocket costs because of their disease, mostly in terms of travel expenses and co-payments for medication.

Conclusions: Given the fact that the majority of surveyed patients have to face financial losses due to their cancer diagnosis which is accompanied by the experience of distress as well as worsened quality of life and health status, there is a need for targeted measures to prevent financial problems and reduce emotional burdens. Further research is required to address this issue.

Clinical trial identification: The trial was approved by the Institutional Research Ethics Committee (approval S-458/2016).

Legal entity responsible for the study: National Center for Tumour Diseases, University Hospital Heidelberg.

Funding: Ipsen Pharma France

Disclosure: All authors have declared no conflicts of interest.

Pancreatic excocrine insufficiency (PEI) in patients (pts) with well-/moderately differentiated neuroendocrine tumours (NETs) treated with somatostatin analogues (SSAs): Incidence and impact on quality of life

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Background: Advanced-wd-NET patients (pts) are commonly treated with SSAs. PEI may be underestimated in trials due to difficulties in distinguishing carcinoid syndrome-related diarrhoea and PEI.

Methods: In this single-institution, prospective, observational study, sequential pts with advanced wd-NET were commenced on SSAs and followed for a minimum of 12 months (or until disease progression). Toxicity was prospectively assessed monthly.

Faecal elastase testing (FE) (for diagnosis of PEI) and quality of life (QoL) questionnaires (QLQ-C30 and QLQ-GI.NET21) were performed 3-monthly.

Results: Of 52 pts recruited (Jan 13-Apr 16), 30 were eligible: median age 65.8 yrs; 58% male; ECOG performance status 0 (42%), 1 (46%) or 2 (12%); primary: small bowel (60%), pancreas (22%), lung (12%) and other (6%). Baseline median Ki-67 was 3.1% (95%CI 1.0-7.9); median time to subsequent death/PD of 19 months.

Conclusions: The final analysis of time to subsequent disease progression/death in patients with metastatic enteropancreatic neuroendocrine tumours (PETs) is ongoing.

Clinical trial identification: NCT00842348

Legal entity responsible for the study: Ipsen Pharma

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Conclusions: SSA-induced PEI occurs in 1-4 pts; clinicians should actively identify and treat.

Legal entity responsible for the study: N/A

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Disclosure: All authors have declared no conflicts of interest.

Final analysis of time to subsequent disease progression/death in patients with metastatic enteropancreatic neuroendocrine tumours progressing under placebo to lanreotide autogel/depot 120mg in the CLARINET open-label extension


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Background: The CLARINET core study established the antitumour activity of lanreotide Autogel 120mg/28 days (LAN) in metastatic enteropancreatic neuroendocrine tumours (NETs). The vast majority of the core study population (96%) had stable disease (SD) at baseline, but the LAN open-label extension (OLE) also included patients with progressive disease (PD), while receiving placebo (PBO) in the core study). Here, we report the final analysis of time to subsequent disease progression/death for patients with PD switched to LAN.

Methods: In the core study, patients with metastatic well-/moderately differentiated non-functioning enteropancreatic NETs received LAN/PBO for 96 weeks or until death/PD (RECIST 1.0). Eligible patients for the OLE (NCT00842348) had SD at core-study end or PD (with PBO only) during the core study. Adverse events (AEs) were recorded at 4-weekly visits. CT/MRI scans from OLE baseline (week 1) and every 24 weeks subsequently were assessed locally for PD (RECIST 1.0). Primary objective: long-term safety. Secondary objective: long-term efficacy, with assessments including PFS and time to subsequent death/PD (from Kaplan–Meier analyses, months approximated as weeks).

Results: 89 patients were treated in both core and OLE studies (42 LAN–LAN [SD, n = 41]; 47 PBO–LAN [SD, n = 13]); 40% of the LAN–LAN vs 47% of the PBO–LAN group had treatment-related AEs. Overall median LAN PFS, based on the intent-to-treat population (n = 101), was 38.5 months. Seven PD events (no deaths) occurred during the OLE in 15 patients entering with SD from the PBO arm of core study. In total, 32 patients with PD whilst receiving PBO in the core study entered OLE (of 59 potentially eligible); NETs were in pancreas in 17 patients, in the lung in 10, in head and neck in 3 and of other/unknown origin in four. Of these patients, 20 had subsequent PD during the OLE and three died; median time to subsequent death/PD was 19.0 months (95% CI 10.1, 26.7).

Conclusions: The final analysis of the CLARINET OLE study suggests benefit with LAN in patients who had experienced PD when receiving no NET-specific treatment (PBO), with median time to subsequent death/PD of 19 months.

Clinical trial identification: NCT00842348

Legal entity responsible for the study: Ipsen Pharma

Funding: Ipsen Pharma

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Efficacy of recombinant human endostatin combined with chemotherapy in advanced pancreatic neuroendocrine tumors

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Background: Dacarbazine or temozolomide, an oral analog of dacarbazine, showed activity against advanced pancreatic NETs when administered alone or in combination with other agents. Targeting pathways involved in angiogenesis, such as VEGF/FRK13 is also active in advanced pNETs. Endostatin is an endogenous angiogenesis inhibitor, rhendostatin combined with chemotherapy prolonged overall survival compared with chemotherapy alone in advanced non-small cell lung cancer.

Methods: 14 patients with histologically confirmed, locally advanced or metastatic pancreatic well-differentiated NETs with radiologic progression within the previous 12 months received the study regimen: Temozolomide was administered orally 150-200 mg/m2/d, d1-7. Dacarbazine and 5-FU were both administered intravenously at a dose of 250mg/m2/d and 100mg/m2/d, respectively, d1-5. rhEndostatin was administrated intravenously at a dose of 15mg/d, d1-14, repeated every 21 days. CT/MRI was performed at baseline and every 3 cycles after initiation of treatment. Radiologic response was classified according to RECIST 1.1 criteria.

Results: Patients received a median of 6 treatment cycles (range, 2 to 8 cycles). Of the 14 patients, 6 patients received temozolomide and 8 received the DTIC > 5-FU combination with rhEndostatin. 5 patients used temozolomide as maintenance therapy, the median maintenance therapy cycles was 6 (range, 2 to 18 cycles). ORR was 45% (CR: 1 patient, PR: 5 patient). DCR was 86%, mPFS was 12 months, overall survival has not been reached. No grade 3/4 toxicity occurred.

Conclusions: rhEndostatin combined with temozolomide or dacarbazine-based chemotherapy was effective in treatment of advanced pNETs and was well tolerated.

Clinical trial identification: NCT01845675

Legal entity responsible for the study: Peking Union Medical College Hospital, Ethic Committee

Funding: None

Disclosure: All authors have declared no conflicts of interest.


Comparison of clinical efficacy of SST analogues therapy (lanreotide autogel vs. octreotide LAR) in treatment of patients with advance, non-resectable pancreatic neuroendocrine tumours (pNETs)

A. Kosalańska-Cwikla1, A. Lewczuk1, J. Paliuk1, L. Savicki1, K. Rzoszkowska-Punka1, M. Robb1, L. Bode1, M. Modrini1, J. Cwikla3

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Background: Use of somatostatin analogues can be considered in pancreatic NET G1/G2 as a first-line therapy. This retrospective study aimed to compare the efficacy of octreotide long-acting release (OCT) and lanreotide Autogel (LAN) in patient with advanced G1/G2 pNETs, comparing between LAN and OCT in naive patients, based on progression free survival (PFS).

Methods: Ninety-two patients with histologically proven G1 or G2 pNETs were retrospectively analyzed (41 men; 51 women; mean age 55.7 years [range 21-87 years]). The patients were assigned randomly to OCT (n = 42) and LAN (n = 50) groups, and the primary endpoint was the time to subsequent death/PD using Kaplan–Meier survival analysis.

Results: Median PFS for all patients was 16.0 months (CI 22.8-34.9) in LAN group vs PFS 22 months (CI 19.5-35.9) vs OCT (CI 18.1-35.5). P = 0.28 (Cox Mantel test). There was no significant difference in group of patients with LAN 22 months (CI 19.5-35.9) vs OCT 7 months (CI 8.2-22.2) P = 0.01. Even higher significant difference was obtained in male group: G2-LAN 21.5 (CI 16.4-44) vs OCT 6.0 months (CI 3.3-14.3). There was no significant difference in female patients: LAN 17.5 mo (CI 15.4-34.8) vs OCT 13 months (CI 8.2-29.4), but the trend favorable LAN over OCT. Additional analysis in patients with liver metastasis showed similar trend, but no significant difference. There was no difference in PFS between groups with LAN in male patients and female patients and those without liver involvement.

Conclusions: Lanreotide Autogel is preferable SST therapy in G2 pNETs, especially in male patients. Additional it seems to be also more effective in female patients but with-out statistical significance. The trend of better efficacy in terms of increase PFS seems to be in favor of LAN in patients with liver involvement as well. There was no significant difference in groups of patients with G1 pNEN and those without liver involvement.

Legal entity responsible for the study: Agnieszka Kosalańska-Cwikla

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Comparison of clinical efficacy of SST analogues therapy (lanreotide autogel vs. octreotide LAR) in treatment of patients with advance, non-resectable pancreatic neuroendocrine tumours (pNETs)

A. Kosalańska-Cwikla1, A. Lewczuk1, J. Paliuk1, L. Savicki1, K. Rzoszkowska-Punka1, M. Robb1, L. Bode1, M. Modrini1, J. Cwikla3

Clinical Oncology, National Institute of Oncology-Marii Sklodowskiej-Curie, Warsaw, Poland, 2Endocrinology, Medical University of Gdańsk, Gdańsk, Poland, 3Wern Laboratories, Wren Laboratories, Branford, CT, USA

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Methods: Ninety-two patients with histologically proven G1 or G2 pNETs were retrospectively analyzed (41 men; 51 women; mean age 55.7 years [range 21-87 years]). The patients were assigned randomly to OCT (n = 42) and LAN (n = 50) groups, and the primary endpoint was the time to subsequent death/PD using Kaplan–Meier survival analysis.

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Conclusions: Lanreotide Autogel is preferable SST therapy in G2 pNETs, especially in male patients. Additional it seems to be also more effective in female patients but without statistical significance. The trend of better efficacy in terms of increase PFS seems to be in favor of LAN in patients with liver involvement as well. There was no significant difference in groups of patients with G1 pNEN and those without liver involvement.

Legal entity responsible for the study: Agnieszka Kosalańska-Cwikla

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Conclusions: Our results suggest a positive impact of various treatment on OS in mNEN elderly patients and the prognostic value of FDG PET and PS ECOG.

Legal entity responsible for the study: Prospective clinical trial are needed to confirm our retrospective data. mNEN elderly patients and the prognostic value of FDG PET and PS ECOG.

Table: 457P Joint distribution of patients according to WHO 2010 classification by the results of the prognostic model

<table>
<thead>
<tr>
<th>WHO 2010 classification</th>
<th>New Prognostic model’s macro groups by Ki67 grading</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>m0,B01, K67 ≤ 2</td>
</tr>
<tr>
<td></td>
<td>m0,B2 Ki67 &gt; 2</td>
</tr>
<tr>
<td></td>
<td>m0,B01 2&lt; Ki67 ≤ 20</td>
</tr>
<tr>
<td></td>
<td>m0,B2 2&lt; Ki67 ≤ 20</td>
</tr>
<tr>
<td></td>
<td>m0,B01 Ki67 &gt; 20</td>
</tr>
<tr>
<td></td>
<td>m0,B2 Ki67 &gt; 20</td>
</tr>
<tr>
<td></td>
<td>m1,0 Ki67 ≤ 55</td>
</tr>
<tr>
<td></td>
<td>m1,0 Ki67 &gt; 55</td>
</tr>
<tr>
<td></td>
<td>m1,0 Ki67 &gt; 55</td>
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<tr>
<td>G1 (Ki67 ≤ 2)</td>
<td>89</td>
</tr>
<tr>
<td>G2 (2&lt; Ki67 ≤ 20)</td>
<td>0</td>
</tr>
<tr>
<td>G3 (20&lt; Ki67 ≤ 55)</td>
<td>0</td>
</tr>
<tr>
<td>G3 (Ki67 &gt; 55)</td>
<td>0</td>
</tr>
</tbody>
</table>

Conclusions: Our results suggest a positive impact of various treatment on OS in mNEN elderly patients and the prognostic value of FDG PET and PS ECOG. Prospective clinical trial are needed to confirm our retrospective data.

Legal entity responsible for the study: Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (I.R.S.T.) IRCCS

Funding: None

Disclosure: All authors have declared no conflicts of interest.

456P Modified staging classification for gastric neuroendocrine carcinomas on the basis of the American Joint Committee on cancer

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Background: The purpose is to explore the value of the seventh edition of AJCC staging and improved AJCC staging in the evaluation of the prognosis of gastric neuroendocrine carcinoma (GNEC).

Methods: We analyzed retrospectively the clinical and pathological data of 427 GNEC patients from SEER database and 129 GNEC patients in single center. AIC and C index were used to evaluate the distinguishing capability of different TNM staging systems.

Results: In SEER database, the 5-year survival rate stratified by AJCC staging of GENC were 68%, 61%, 46%, 22%, 21%, and 10% respectively. While in single center, the 5-year survival rate of different stages were 100%, 60%, 27%, 16%, 22%, and 0% respectively. From the survival curve analysis, there are significant cross-overs between the IIIB survival curves of SEER database as well as single center and those of IIIA and IIB. In SEER database, the I staging and the age of disease diagnosis were independent factors affecting the prognosis of IIB patients. According to the T staging, the IIB was divided into four subgroups: T1N1, T2N1, T3N1, and T4N1. According to the principle of similar survival rate, the new AJCC staging is composed of different stages: m1(T1N0M0), n1T1N1M0, T2N0M0, n1T2N1M0, T3N0M0, n1T3N1M0, T4N0M0, and n1T4N1M1. The survival curve of the new AJCC staging showed less crossover per stage, obtaining a smaller AIC value (0.795 vs. 0.7421). It is discovered that through employing the data of single center as external validation, the new AJCC staging can better distinguish different TNM staging.

Conclusions: Dividing IIB of the seventh edition of AJCC staging into various sub-stages has significant prognostic value and the new AJCC staging can better distinguish the stages of GNEC. Legal entity responsible for the study: Changming Huang

Funding: None

Disclosure: All authors have declared no conflicts of interest.

457P Predictive factors in GEP-NEN: The integrated role of Ki67, beta-catenin and morphology

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Background: The WHO 2010 classification divides gastro-entero-pancreatic neuroendocrine tumors (GEP-NENs) into G1, G2 and G3, according to Ki67 and/or mitotic index. Several studies have proposed to further divide G3 diseases in at least two subgroups, defined by Ki67 and/or morphological features. We investigated the morphological or immunohistochemical features associated with poorer prognosis and weather the G3 category could be further divided according to such features.
Methods: We evaluated 314 consecutive GEP-NEN patients. Surgical specimens of primitive tumors were assessed for morphology (m0: well-differentiated; m1: poorly-differentiated), Ki67 and beta-catenin (B01 absent or not-nuclear localization, B2 nuclear localization). These features were correlated with overall survival (OS) and disease-free survival (DFS) after surgery by means of Cox multivariable models. The model performance was evaluated by means of Harrell's C index.

Results: Median follow-up was 84 months (95% CI 74-103). Based on Ki67 only, the WHO 2010 classification allowed to distinguish three cases with different prognosis (5-year OS: 72.2%; 95% CI 64.3% to 79.1%; 5-year DFS: 67.6%; 95% CI 56.1% to 77.7%). As Ki67 was continuous variable, and by including also morphology and beta-catenin in the multi-variable OS model, patient-specific estimates were obtained, thereby improving the prognostic classification, particularly for G3 patients, which could be split in further sub-groups (Table). Harrell's C index was 0.86. Similar results were obtained for DFS.

Conclusions: WHO 2010 classification stratifies the risk of OS and DFS for G1 and G2 diseases. On the other hand, the risk of death for G3 disease varies according to Ki67 values, morphology and beta-catenin. Morphology has the strongest predictive power, segregating two macro groups in which beta-catenin has a lower differential effect while a prognostic gradient by Ki67 (up to Ki67 = 55) is evident.

Legal entity responsible for the study: FONDAZIONE IRCCS Istituto Nazionale Tumori, Milano Ethical Committee Approved 48/16

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Follow-up and recurrence in resected gastroenteropancreatic neuroendocrine tumours: A population-based study

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Background: Neuroendocrine tumours (NETs) are uncommon. Little data exist to guide follow-up in resected disease, with no consensus regarding the optimal follow-up frequency or modality. Follow-up imaging regimens are extrapolated from other gastrointestinal tumours. As NETs are heterogeneous, this may result in both over-use and underuse of investigations in patients.

Methods: A population-based retrospective cohort study using linked data from the Institute for Clinical Evaluative Sciences and the Ontario Cancer Registry (capturing more than 99% of incident cases in Ontario) was conducted to evaluate patients diagnosed with gastroenteropancreatic NETs in Ontario, Canada from 1994 to 2012. Recurrence-free survival and the frequency of cross sectional imaging (abdominal computed tomography (aCT), magnetic resonance imaging (aMRI) and ultrasound (aUS)) were the main outcomes.

Results: Nine hundred and thirty-six patients were identified with median follow-up 47 months. The mean age was 59, 51% were female, and distribution of primary cancers was: small intestine 47%, pancreas 20%, large intestine 21%, rectum 4%, stomach 6.6%. The median survival time to a composite outcome of recurrence or death was 7.2 years, and 9.5 years of censoring on death. The cumulative incidence of recurrence was 8.4% (95% CI 6.9% to 10.3%) within one year, 33.2% (95% CI 30.4% to 36.0%) within five years, and 48.5% (95% CI 44.4% to 52.4%) within 10 years. The rate of recurrence significantly increased with age (HR = 1.529 for age 50-70 compared to < 50, p = 0.0003) and pancreatic primary (HR = 1.663, p = 0.0086), but not income quintile (p = 0.1071), rurality (p = 0.1931) or gender (p = 0.3878). The rate of use of aCTs, aMRs and aUS decreased over time, from 1.84 per 100 patient-months in the first year to 0.22 at 48 months. On average, 1.59 abdominal CTs per patient were performed in the first year, 0.85 in the second year and 0.52 in years 3-5.

Conclusions: Unlike colon cancer, significant numbers of NETs recur between 5-10 years after curative surgical resection. These data support the lengthening of follow-up for resected NETs to a minimum of 5 years post surgical resection, as well as the impact of imaging on early detection of recurrence and survival outcomes.

Legal entity responsible for the study: Sunnybrook Research Institute

Funding: AGITG

Disclosure: D. Chan: Travel support from Novartis; honoraria from Ipsen. E. Segovia: Honoraria from Roche, Bayer, Ipsen and Pfizer; travel support from Merck Serono; honoraria from Roche and Ipsen. S. Singh: Honoraria and travel funding from Ipsen, Pfizer and Novartis. All other authors have declared no conflicts of interest.

Elevated levels of 5-HIAA and CgA in patients with PanNETs from the CLARINET Study


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8Gastroenterology and Hepatology, Endocrinology & Metabolic Diseases, Charite – University Medicine Berlin, Berlin, Germany

Background: While carcinoids frequently synthesize, and secrete serotonin into the circulation, and 5-HIAA is a common biomarker in the carcinoids, measurement of 5-HIAA in non-carcinoid PanNET patients (i.e. no hormone-related symptoms or non-functional) is not routinely recommended by international guidelines. The incidence of serotonin-producing PanNETs may be underestimated, with potential impact on clinical outcome when serotonin levels remain elevated. We sought to characterize 5-HIAA and CgA levels in PanNET patients who participated in the large placebo-controlled phase III CLARINET Study.

Methods: Evaluable data available for urinary 5-HIAA and serum CgA for patients with PanNET in CLARINET study were analyzed. Urinary 5-HIAA and Serum CgA were assessed at baseline and every 12 weeks thereafter through Week 96. Changes from baseline in urinary 5-HIAA and serum CgA levels were calculated using a non-parametric Wilcoxon 2-sample test. Biochemical response for urinary 5-HIAA or serum CgA was defined as baseline > upper limit of normal (ULN); ≤ ULN decrease of ≤ 50% in patients on placebo at the last available value (p = 0.03). Among patients with baseline CgA > ULN, biochemical response was achieved in 69% (19/28) of lanreotide-treated patients compared with 54% (9/17) in patients on placebo at the last available value (p = 0.0002). Limited sample sizes precluded robust analysis for potentially significant differences in the lanreotide vs. the placebo group among patients with elevated biomarkers at baseline and biochemical response.

Conclusions: The percentage of patients with elevated urinary 5-HIAA was unexpected. The concept of PanNET and secretion of serotonin may need to be redefined. The potential of 5-HIAA and CgA as biomarkers of response and follow-up in nonfunctioning PanNET is alluring, but requires further study. Data from additional prospective studies are needed to impact clinical practice guidelines.

Clinical trial identification: NCT00353496

Legal entity responsible for the study: Ipsen Biopharmaceuticals

Annals of Oncology


461P The prognostic value of cytokeratin 7, 19, thyroid transcription factor-1 and CD117 expression in lung neuroendocrine tumors of various grades
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Background: Neuroendocrine tumors of the lung (NETL) are a wide range of tumors with various malignancy grades and prognosis.

Methods: We performed immunohistochemical assessment of the diagnostic biopsies and surgical specimens from 205 patients with NETL aged 55 ± 14 years and identified 61 (29.8%) typical carcinoids (TC), 44 (21.3%) atypical carcinoids (ATC), 84 (41.1%) small cell neuroendocrine carcinomas (SCNEC) and 16 (7.8%) large cell neuroendocrine carcinomas (LCNEC). Markers of neuroendocrine differentiation (synaptophysine, chromogranine A and CD56) and cytokeratins (CK) 7 and 19, thyroid transcription factor-1 (TTF-1), CD117 were used.

Results: Most often, the expression of CK7 and CK19 was found in LCNEC (71.4%, 10/14) and ATC (91.7%, 40/44) (respectively). CD117 was expressed less frequently, in ATC and SCNEC (52.8%, 19/37 and 52.4%, 22/43; 43.9%, 29/66 and 68.2%, 45/66 of cases, respectively), whereas in TC it was rare (13.3%, 6/45 and 19.4%, 11/57 respectively). The rates of CK7 and 19 expression were significantly lower in the TC, compared to the SCNEC and LCNEC (p < 0.01, γ). The expression of TTF-1 was very rare in the TC (11.6%, 4/36 cases) and significantly more often in ATC (60.5%, 23/38) and in SCNEC and LCNEC (79.2%, 57/72 and 75.9%, 9/12 of cases, respectively). TTF-1 expression was significantly less frequent in typical than in ATC, SCNEC and LCNEC (p < 0.01, γ). The expression CD117 was absent in the TC (0%, 0/27), very rare in the ATC (17.4%, 4/23) and significantly more often in SCNEC and LCNEC (97.9%, 43/47 and 42.8%, 3/7 of cases, respectively).

Conclusions: Expression of TTF-1, CK7, CK19 and CD117 in the NETL is characteristic for a less differentiated cell immunophenotype and allows for identification of the risk group with unfavorable clinical outcome among low-grade TC and ATC.

Legal entity responsible for the study: L. Gurevich

Funding: None

Disclosure: All authors have declared no conflicts of interest.

462P A nomogram based on tumor-associated neutrophil-to-lymphocyte ratio to predict survival prognosis for patients with gastric neuroendocrine neoplasms
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Department of Gastric Surgery, Fujian Medical University Union Hospital, Fuzhou, China.

Background: This study investigated the predictive value of the tumor-associated neutrophil-to-lymphocyte ratio (TA-NLR) on clinical outcomes for patients with gastric neuroendocrine neoplasms (g-NENs) after radical surgery.

Methods: Data from 142 patients who were diagnosed with g-NENs and underwent radical gastrectomy at our department from March 2006 to March 2015 were prospectively collected and retrospectively analyzed. Receiver operating characteristic curve analysis was used to identify the optimal value for TA-NLR. Univariate and multivariate survival analysis were used to identify predictive prognostic factors for g-NENs. A nomogram was adopted to predict RFS and OS after surgery.

Results: TA-NLR was not significantly associated with clinical characteristics (all P > 0.05). TA-NLR significantly correlated with tumor recurrence, especially with liver and lymph node metastasis (both P < 0.05). A multivariate Cox regression analysis identified the TA-NLR as an independent prognostic factor for recurrence-free survival (RFS) and overall survival (OS) (both P < 0.05). The concordance index (C-index) of the nomograms, including the TA-NLR, Ki-67 index and lymph node ratio, for RFS (OS) was 0.788 (0.759) and was higher than the C-index of the traditional TNM staging system (0.672/0.663).

Conclusions: TA-NLR was an independent prognostic factor for patients with g-NENs regarding RFS and OS. Nomograms with the TA-NLR, Ki-67 index and lymph node ratio had a superior ability to predict clinical outcomes for postoperative g-NENs patients, as well as the traditional TNM staging system.

Legal entity responsible for the study: Changming Huang

Funding: None

Disclosure: All authors have declared no conflicts of interest.

463P Plasma protein fingerprinting and machine learning for the diagnosis of small intestinal neuroendocrine tumors: The nordic NET biomarker group EXPLAIN study
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Background: Small intestinal neuroendocrine tumors (sNETs) are notoriously difficult to diagnose, especially in an early stage. The EXPLAIN study aimed to investigate
Conclusions: Both a high level of sensitivity and specificity (0.9) were obtained using proton pump inhibitor treatment (PPI): 42.37 (86.62), in 21 NET patients with PPI. Legal entity responsible for the study: our multi plasma protein strategy combined with SSLT for the diagnosis of siNET.

Disclosure: All authors have declared no conflicts of interest.

Table: 463P Comparison of SSLT models

<table>
<thead>
<tr>
<th>Model</th>
<th>SVM – Radial</th>
<th>SVM – Linear</th>
<th>Random Forest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuracy (95% CI)</td>
<td>0.8429 (0.7362, 0.9193)</td>
<td>0.8714 (0.7699, 0.9193)</td>
<td>0.8857 (0.7872, 0.9493)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.7647</td>
<td>0.7941</td>
<td>0.8824</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.9167</td>
<td>0.9444</td>
<td>0.8889</td>
</tr>
<tr>
<td>AUC</td>
<td>0.9191</td>
<td>0.9428</td>
<td>0.9404</td>
</tr>
</tbody>
</table>

Conclusions: Both a high level of sensitivity and specificity (0.9) were obtained using our multi plasma protein strategy combined with SSLT for the diagnosis of siNET. Further development of the machine learning model is ongoing.

Legal entity responsible for the study: Peter Myrenfors Ipsen

Funding: Ipsen

Disclosure: All authors have declared no conflicts of interest.

464P

CXC4R inhibition by ulocuplumab prevents EMT of pNET cells in vitro

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Background: NETs overexpress CXC4R. We have previously shown that stimulation of CXC4R by its ligand SDF-1 promotes EMT and increases the distant tumor spread of NET cells. Ulocuplumab (Ulo) is a fully human IgG4 mAb designed to inhibit the binding of SDF-1 to CXC4R. We investigated the effects of Ulo in preventing pNET spreading in vitro.

Methods: Complement-dependent cytotoxicity (CDC), Ab-dependent cell cytotoxicity (ADCC), Ab-dependent cell phagocytosis (ADCP) and direct Ab-induced apoptosis were investigated using three pNET cell lines (BON1, CM, GCP1) treated with Ulo. Transcriptome profiling was performed by RNASeq following incubation with SDF-1 in the presence or absence of Ulo. Flow cytometry was used to characterize the EMT-related phenotype of NET cells, as well as their expression of immune checkpoints in response to EMT-inducing stimuli. Migration and invasion of pNET cells towards liver and bone fragments was evaluated by transwell assays. The effects of Ulo on the intracellular signaling activated by CXC4R stimulation were investigated by western-blot (WB), while confocal microscopy assessed the nuclear expression of CXCR4 after high-quality nucleocytoplasmic fractionation.

Results: Ulo failed to induce CDC, ADCC and ADCP in pNET cell lines, in absence of significant direct tumor cell killing. Ligand stimulation of CXC4R promoted an EMT-like transcriptional shift (upregulation of SNAIL, ZEB1, MAD2Z), which was abrogated by Ulo. Treatment with SDF-1 induced cadherin switch, but was unable to alter the membrane expression of immune checkpoints including PD-L1, PD-L2 and CD80. Both in vitro migration and invasion of pNET cells towards liver and bone were significantly suppressed by CXC4R blockade. Stimulation of CXC4R induced the phosphorylation of Akt, ERK, and NF-κB, resulting in Vimentin overexpression as well as acquisition of mesenchymal patterns including enhanced spindle index. These effects, inhibited by Ulo, were paralleled by a substantial enrichment of CXC4R on the nuclear membrane.

Conclusions: Ulo suppresses EMT in pNET cell lines by both disabling the intracellular signaling downstream CXC4R activation and preventing its nuclear localization. The pathophysiology of nuclear CXC4R needs to be investigated.

Legal entity responsible for the study: Bayer

Funding: Bayer

Disclosure: All authors have declared no conflicts of interest.

465P

Interim baseline characteristics from RIFTOS MKI, a global non-interventional study assessing the use of multikinase inhibitors (MKIs) in the treatment of patients with asymptomatic radioactive iodine-refractory differentiated thyroid cancer (RAI-R DTC): A European subgroup analysis

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Background: RIFTOS MKI was designed to compare the time to symptomatic progression from study entry in patients with RAI-R DTC for whom there was a decision to treat or not to treat with an MKI in the real-life setting. Here, we report interim baseline characteristics for a subgroup of patients from Europe.

Methods: RIFTOS MKI is a non-interventional study enrolling patients from USA, Japan, Europe, and rest of the world with asymptomatic RAI-R DTC. The decision to initiate MKIs at study entry was at the discretion of the treating physician. Final analysis will be performed once 700 patients have been enrolled and the last enrolled patient has been followed for 24 months.

Results: Of the 80 patients enrolled from Europe, the median duration of observation was 165 days; 51% were male and the median age was 67 years. Most patients had an ECOG performance status of 0 or 1 (96%) and distant metastasis at initial visit (81%). The most frequent histology was papillary (61%). The median time from initial diagnosis to study entry was 7.7 years. RAI refractoriness was mainly due to lack of RAI uptake (79%) and the median time from RAI classification to initial visit was 25 months. The average dose per RAI treatment and median cumulative activity of RAI were 4.6 and 13.0 GBq, respectively.

Conclusions: The interim baseline characteristics results presented here are similar to those previously reported in phase III studies. The study is ongoing.

Clinical trial identification: NCT0230344

Legal entity responsible for the study: Bayer

Funding: Bayer

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All authors have declared no conflicts of interest.

Background: MANEC is a rare entity and evidence on its prognosis and management is limited.

Methods: Demographic/clinicopathological survival data of consecutive patients (pts) with diagnosis of MANEC (2018 WHO criteria) from 4 European centres were retrospectively reviewed.

Results: Fifty-three pts were identified (01/06-03/17); median (med) age 62 yrs (range 34-89); male, 70%, ECOG PS 0-1; 60%, with primary tumours from small/large bowel in 34 (66%), oesophagus/pharynx/pancreas/biliary tract in 5 (9.5%); unknown (UNK) 1 (2%). Forty percent had a comorbid evaluation (ACE)-27 score of ≥0. The neuropeptide (NE) component (predominant histology in 40%) was poorly-differentiated (PD) in 45 (85%); B1/B2/B3 (5%); synaptophysin (100%), chromogranin A (CgA) (38.5%) and CDX2 (51%). Histology was PD NE in 64% from recurrent/metastatic sites (n = 14 pts). Of 28 (53%) pts with localised disease (LA), 26 (93%) had curative surgery (7 had neoadjuvant chemo-radiation therapy (CRT); 6 advanced CT, 1 peri-operative CT, 1 (3.3%) had definitive CRT and 1 (3.3%) had UNK management. IHC negativity for CgA and CDX2 was prognostic for better PFS and OS (both p < 0.05); IHC negativity for NE and CgA was prognostic for better OS (both p < 0.05). Conclusions: PD NE histology in MANEC was predominant in both diagnostic and recurrent/metastatic tumour samples. Active treatments were offered to most pts but more effective therapy is clearly needed.

Legal entity responsible for the study: The Christie NHS Foundation Trust

Funding: The Christie

Disclosure: All authors have declared no conflicts of interest.

467P Incidence of adrenal gland tumor as a second primary malignancy: SEER based database

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Background: Adrenal gland tumors are sporadic and heterogeneous, with an incidence (excluding childhood neuroblastoma) of 0.05% in the US. Advances in cancer treatment in the last few decades have resulted in increased survival in most paediatric and adult cancer types. The aim here is to report the incidence of adrenal gland tumors as a second primary tumor based on data from the SEER database.

Methods: Data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute, using the SEER*stat software (version 8.3.2) was obtained. All cancer sites using the Multiple Primary Standardized Incidence Ratios ‘MP-SIR’ session were selected. SEER 13 Regs Research Data from1992 to 2013 was used.

Results: Data from a total of 2,887,468 persons with cancer were reviewed, 117 of whom had suffered second primary adrenal tumors. One of these patients had two events of adrenal cancer as a second primary, resulting in a total of 118 incidences. The overall standardized incidence ratio (SIR) of adrenal gland tumor as a second primary was 1.49. A high percentage of this event was found in elderly patients, especially those with metastatic disease. Most of these patients were treated with neoadjuvant CT followed by concurrent RT-C (n = 9). Either pulsed-dose rate (PDR) brachytherapy (n = 4) or colpo-hysterectomy (n = 3) was performed according to tumor response. Adjuvant CT was performed to 3 pts in this subgroup (mean number of cycle: 3). 9 pts were treated with chemotherapy. Median follow up was 9.2ms (range 1.1-28ms). 2 PTS received TMZ for more than 2 years and other 2 PTS for more than 1 year. Median PFS and OS were not reached (95% CI = 4 months-n.a, 6.2ms-n.a, respectively). Urinary metanephrines levels seem to correlate with response. Hypertension decreased significantly in 5 Pts during TMZ treatment. No grade 3-4 toxicity was recorded.

Conclusions: TMZ is an active and safe treatment for MPP, regardless of previous anticancer treatment modalities.

Funding: None

Disclosure: All authors have declared no conflicts of interest.

468P Neuroendocrine carcinoma of the uterine cervix: A retrospective monocentric study

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Background: Neuroendocrine cervical carcinoma (NECC) is a very aggressive and rare disease. To date, only 2 prospective studies with scarce patient numbers have been reported in the literature. Here we study a NECC patients (pts) cohort treated with current anticancer treatment modalities.

Methods: All pts with NECC were retrieved from 1996 to 2013 in our institute (n = 14). 3D-conformal radiation therapy combined to concomitant chemotherapy (RT-CT) was performed to all pts. Chemo- regimen (CT) was cisplatin plus etoposide or carboplatin plus etoposide. Mean total dose to clinical target volume (CTV) was 48 Gy.

Results: Pts and treatments characteristics. Mean age was 48.5 years old. Most of pts had a loco regional disease (n = 11): stage IA (n = 1), IB (n = 1), IIA (n = 2) and IIB (n = 7). 3 pts were stage IVB. Pelvic and/or lombo-aortic lymph nodes involvement was observed in 43.8% pts (n = 6). Among them, 3 pts were treated with an extended lombo-aortic radiation field. Among the entire cohort, 2 treatment modalities were distinguished: (i) most of pts were treated with neoadjuvant CT followed by concurrent RT-CT (n = 9). Either pulsed-dose rate (PDR) brachytherapy (n = 4) or colpo hysterectomy (n = 3) was performed according to tumor response. (ii) Colpo hysterectomy followed by concomitant RT-CT and PDR brachytherapy (n = 1), adjuvant CT delivered to 1 patient (3 cycles). Pts outcome. Median follow up was 10 years (range,
2 FDA-approved tyrosine kinase inhibitors (TKIs), which might not be affordable for most of the Chinese patients (pts). Apatinib is an oral TKI targeting VEGFR-2, with a patient assistance program available in China. It achieved a quick Tg decline of 21% 2 weeks later and an objective response rate (ORR) of 90%, showing promising efficacy in RAI-DTC (Lin et al, ATA 2016, Short Call Poster 65; Lin et al, Oncotarget, Epub Feb 02, 2017). Thus, this study aimed to further evaluate the efficacy and safety of apatinib in treating RAI-DTC.

Trial design: This study is a multicentre, randomised, double-blind, parallel-group, placebo-controlled, phase III trial in China. Adult pts with locally advanced or metastatic RAI-DTC are eligible. The inclusion criteria include at least one measurable lesion; disease progression within the past 12 months; and ECOG PS 0–2. Pts are defined as RAI-DTC if they have target lesion(s) without iodine uptake, received one RAI treatment (>3.7 Gbq [>100 mCi]) but progressed within the past 12 months, received two RAI treatments or more with a time interval of less than 12 months and progressed at least 12 months later); or received cumulative RAI activity over 22.2 Gbq (>600 mCi). Previous targeted therapy is not allowed. Enrolled patients will be randomly assigned to receive apatinib (500 mg qd) and placebo, respectively. Four weeks is defined as one cycle. Dose increase to 750 mg and dose reduction to 250 mg are allowed. The primary endpoint is progression free survival. The secondary endpoints include disease control rate, ORR, duration of response, changes in serum Tg and TgAb concentration, quality of life, and safety. A multiple Cox proportional hazards model is used to evaluate the hazard ratios after adjusting iodine uptake, metastatic lesion site, gender, and age. 118 pts will be recruited assuming a 106.9% increase in median PFS in the apatinib arm compared with the placebo arm. As of 2nd May 2017, 3 eligible patients have been enrolled.

Clinical trial identification: NCT0348877 (Release date: February 7, 2017)

Legal entity responsible for the study: Yansong Lin

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Background: The International Duration Evaluation of Adjuvant chemotherapy (IDEA) collaboration was established to combine data from 6 randomized trials to assess whether 3-month (3M) of oxaliplatin/fluoropyrimidines-based adjuvant chemotherapy is non-inferior to 6-month (6M) for 3-year disease-free survival (DFS) in stage III colon cancer (CC).

Methods: IDEA France randomized patients (pts) between 3M and 6M of chemotherapy with mFOLFOX6 or XELOX (physician choice). DFS was estimated using the Kaplan–Meier method and described using a 3-year DFS rate with 95% confidence interval (CI). Cox-proportional-hazard models were performed to estimate the hazard ratios (HRs) and 95% CIs. We present here the results in the modified ITT (mITT) population receiving at least one dose of treatment and modified per-protocol (mPP) pts receiving 3M in the 3M arm and >5M in the 6M arm populations. Subgroups and long-lasting neuropathy results are also reported here.

Results: From May 2009 to May 2014, 2022 pts were randomized from 129 centers and 2010 (99%) and 1757 (87%) were included in the mITT and mPP populations, respectively. With a median follow-up of 4.3 years, the 3-year DFS rate was 72% and 76% (HR = 1.24; 95% CI 1.05–1.46, p = 0.01) for the 3M and 6M mITT populations, respectively and 72% and 78% (HR = 1.36; 95% CI 1.14–1.63, p < 0.0008) for the 3M and 6M mPP populations. In the mITT mFOLFOX6 treated population (96% of pts), 3-year DFS was 81% (3M) and 83% (6M) for T1/T2-3N1 pts (N = 1106, HR = 1.15 95%CI 0.89–1.49 and 38% (3M) and 66% (6M) for T4a/N2 pts (N = 702, HR = 1.44 95%CI 1.14–1.82). Grade ≥1 neuropathy was observed in 36% and 67% of pts (p < 0.0001) in the 3M and 6M arms, respectively. With a median follow-up of 3.6 years, final residual grade ≥1 neuropathy was 2.8% and 7.4% (p < 0.0001), in the 3M and 6M arms, respectively.

Conclusions: The IDEA France study confirmed, with 90% of pts treated with mFOLFOX6, that 3M adjuvant chemotherapy is superior to 6M. However, this difference was not significant in the mITT and mPP ITT-3N1 populations suggesting that the 3M of mFOLFOX6 regimen could be an option for these pts. Clinically relevant (grade ≥1) neuropathy was significantly higher in the 6M arm, with long-lasting neuropathy in 7.4% of pts.

Clinical trial identification: Registration Number (European Union Drug Regulating Authorities Clinical Trials): 2009-01584-16

Legal entity responsible for the study: CERCOR - Groupe Cooperateur Multidisciplinaire en Oncologie

Funding: French Ministry of Health and French National Cancer Institute (InCa)

Disclosure: J. Taieb: Advisory board or Board of directors: Sanofi, Baxalta, Roche, Merck, Amgen, Lilly, Celgene. F. Bonnetain: Advisory board or Board of directors: Roche, Ipsen, Genti, Nestle, Novartis, corporate-sponsored research: Novartis, Roche. L. Mineur: Advisory board or Board of directors: Amgen, Sanofi, Bayer, Roche, corporate-sponsored research: Sanofi, Merck, Chugai, J. Bournia: Advisory board or Board of directors and honorarium: BMS, Roche, Boehinger Ingelheim, AstraZeneca. D. Vernerey: Honorary: Janssen, Celgene. Advisory board: HalloDx, C. Lepere: Advisory board or Board of directors: Ipsen, O. Bouche: Advisory board or Board of directors: Merck Serono, Roche, Amgen, Y. Tsuda: Advisory board or Board of directors: Roche, Bayer, Amgen, Lilly. T. André: Advisory board or Board of directors: BMS, Amgen, Roche; corporate-sponsored research: BMS, Roche; honoraria: Baxter, Bayer, Lilly, MSD, Mundipharma, Novartis. All other authors have declared no conflicts of interest.

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Annals of Oncology

4750 mFOLFOXIRI + panitumumab versus FOLFOXIRI as first-line treatment in patients with RAS wild-type metastatic colorectal cancer (mCRC): A randomized phase II VOLFI trial of the AIO (AIO-KRK0109)

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Background: Triple chemotherapy with an anti-EGFR promoted promising activity with some safety concerns in advanced phase II trials. The randomized VOLFI trial evaluated activity and safety of mFOLFOXIRI + panitumumab versus FOLFOXIRI in ECOG 0-1, primarily non-resectable mCRC patients.

Methods: Prospective 2:1 randomized, multi-center, phase II trial comparing mFOLFOXIRI (Oxalipatin 85 mg/m2, Irinotecan 150 mg/m2, S-FU 3000mg/m2 cont. 48h, LV 200 mg/m2) + Panitumumab 6 mg/KG (arm A) with FOLFOXIRI (Ox 85 mg/m2, Ir 165 mg/m2, S-FU 2400mg/m2, arm B), both qw2. Cohort 1: irritable mCRC; cohort 2: chance of secondary resection of metastatic lesions. Primary endpoint was ORR, secondary endpoints were secondary resection rate (cohort 2), DCR, PFS, OS, toxicity, quality of life. Financially supported by an unrestricted grant from Amgen.

Results: A total of 96 patients were randomized (63 arm A, 33 arm B). In arm A and B 20 (31.7%) and 11 (33.3%) patients belonged to cohort 2, respectively. ORR was 85.7% in arm A and 54.9% in arm B (p = 0.0113, 95%: CI 0.780-1.000). DCR was 96.8% in arm A and 78.8% in arm B (p = 0.0071, OR 8.212). In arm A and B 53 (84.1%) and 25 (75.8%) tumors were left sided, 10 (15.9%) and 6 (18.2%) were located in the right colon, respectively. ORR in Arm A was 90.6% versus 60.9% (p = 0.0288, OR 6.400) and in Arm B 60.9% versus 50% (p = 0.0459) for left and right located CRC, respectively. ORR between arms A and B comparing left and right sided CRC was 90.6% versus 60.9% (p = 0.0038, OR 6.400, 95%: CI 1.889-21.679) and 60.9% versus 50% (p = 0.0511), respectively. Secondary resections in cohort 2 were 60% (n = 12) and 36.4% (n = 4) in arms A and B, respectively. Serious adverse events grade 3-5 occurred in 43.2% and 22.4% in arms A and B, respectively (p = 0.0496).

Conclusions: Panitumumab plus mFOLFOXIRI results in significantly higher response rates compared to FOLFOXIRI in wild-type mCRC. Response rates, however, are differential according to tumor sidedness. High secondary resection rates were observed. Toxicity is manageable in younger fit patients with ECOG 0-1. PFS, OS, QL and TR data are still immature and will be presented at the meeting.

Clinical trial identification: NCT01328171

Legal entity responsible for the study: AIO

Funding: AIO

Disclosure: M. Geisler: Honoraria and advisory board from Amin. All other authors have declared no conflicts of interest.

4770 Bevacizumab (Bv) or cetuximab (Cet) plus chemotherapy after progression with bevacizumab plus chemotherapy in patients with wild-type (WT) KRAS metastatic colorectal cancer (mCRC): Final analysis of a French randomized, multicenter, phase II study (PRODIGE 18)

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Background: Second-line treatment with chemotherapy plus Bv or Cet is now established as a valid option in mCRC. The main objective of this French multicenter, randomized open phase II trial, was to evaluate the Progression Free Survival (PFS) rate at 4 months with chemotherapy plus Bv or Cet in patients with disease progression after Bv plus chemotherapy.

Methods: The main eligibility criterion was disease progression after bevacizumab + 5-FU with irinotecan or oxaliplatin in patients with WT KRAS exon 2 mCRC. Patients were randomized in Arm A (FOLFIRI or mFOLFOX6 plus Bv) or in Arm B (FOLFIRI or mFOLFOX6 plus Cet); the chemotherapy doublet was chosen according to the first line (cross over). Analyses were performed in ITT population. They were repeated on the KRAS+ – NRAS WT population in the treatment and the triple negative population (KRAS, NRAS, and BRAF negative).

Results: From October 2010 to May 2015, 133 patients were included in 25 sites (1 patient ineligible): 85 males (64%), PS 0 (74, 54%), unknown (3, 4%). The 4-month PFS rate was 80.3% (95%CI 76.8% - 83.8%) in Arm A and 66.7% (95%CI 53.6% - 78.4%) in Arm B. Median PFS was 7.1 months in Arm A vs 5.6 months in Arm B (p = 0.096). Median OS reached 15.8 months in Arm A vs 10.4 months in Arm B (p = 0.073). Tumors samples were collected by a central laboratory and 95 were analyzed using the KRAS/BRAF mutation analysis panel kit (KRAS exon 2,3,4 and BRAF V600E) and KRAS mutation detection kit (exons 2,3,4, Entrogen). On the whole, 81 patients were KRAS and NRAS WT (41 in Arm A and 40 in Arm B). Median PFS was respectively 7.8 months and 5.6 months in Arm A and Arm B (p = 0.076); median OS was 21.0 months in Arm A vs 18.7 months in Arm B (p = 0.324). 73 were negative for the 5 genes (n = 36 and 37). Their median PFS were 8.2 months in Arm A vs 5.7 months in arm B (p = 0.160). Median OS was 21.1 months vs 12.6 months (p = 0.385).

Conclusions: PRODIGE 18 study is in favor of continuation beyond progression with chemotherapy cross over in WT RAS mCRC initially treated with first-line Bv plus chemotherapy.

Legal entity responsible for the study: UNICANCER
**Abstracts**

**4780 Efficacy and safety of Sym004 in refractory metastatic colorectal cancer with acquired resistance to anti-EGFR therapy: Results of a randomized phase II study (RP5)**

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**Background:** Sym004, a mixture of 2 anti-EGFR monoclonal antibodies (mAbs), was shown to be active in a prior PI2/J trial in refractory mCRC. Due to its unique mode of action, Sym004 was developed for overcoming of acquired resistance to anti-EGFR antibodies.

**Methods:** 254 patients (pts) were entered to an open label, multinational, 3-arm (1:1:1) RP2S comparing 2 regimens (12 mg/kg [A] or 9 mg/kg loading dose followed by 6 mg/kg [B]) of weekly Sym004 vs investigator choice (IC) of 5-FU, capecitabine, or best supportive care [C]. Standard eligibility criteria were used; pts were to be refractory to any prior anti-EGFR treatment and to have measurable mCRC (>10 mm). The primary endpoint was the best overall response (BOR) at median follow-up of 8.6 months (m). 102 pts were evaluable for BOR (Arm A = 33, Arm B = 33, Arm C = 36). At the interim analysis (IA), efficacy was assessed using RECIST v1.1, while safety was evaluated according to NCI CTCAE v4.0.

**Results:** Demographic and baseline parameters were well balanced. The Sym004 adverse event (AE) profile was typical although frequency/severity of dermatologic AEs or hypomagnesemia was higher and GI AEs appeared lower than with approved anti-EGFR mAbs. Arm B was better tolerated than Arm A. OS in the ITT population and exploratory subgroups are presented. The primary outcome of the study was negative due to unexpected outcomes of Arm C. Arm B (9/6 mg dose) was not only better tolerated over 12/6 mg (Arm A), but also was associated with improved survival. Biomarker-specific analyses evaluating pts with double-negative (DN) (no RAS mutant allele frequency >20% in circulating tumour cell ctDNA; no BRAF V600E or triple-negative (TN) (no EGFR extracellular domain mutation in ctDNA) mCRC demonstrated markedly prolonged survival and established the 9/6 regimen as well-tolerated and active in DNmCRC (OS increased 3.5 m) and TNmCRC (OS increased 5.5 m).

**Conclusions:** Although the study was negative in ITT population, treatment with Sym004 was associated with remarkable response when compared with any 4th-line treatment of mCRC. The promising results in the molecularly selected population provide guidance to design a pivotal ctDNA-guided pivotal trial in EGFR inhibitor refractory mCRC.

**Clinical trial identification:** NCT02083653 or EMR200637-002

**Legal entity responsible for the study:** Symphogen

**Funding:** Symphogen

**Disclosure:** J. Tabernero: Advisory boards: Amgen, Bayer, Boehringer Ingelheim, Celgene, Chugai, Genentech, Lilly, MSD, Merck Serono, Novartis, Pfizer, Roche, Symphogen, Taiho, Takeda. F. Ciardiello: Advisory boards: Roche, Merck, Lilly, BMS, Pfizer, Amgen, Bayer. C. Montagut: Advisory boards: Amgen, Bayer, Merck Serono, Sanofi. Symphogen: C. Ding, T. Tuxen Poulsen, M. Kragh, I.D. Horak: Employee of Symphogen. S. Kopetz: Advisory boards: Amgen, Merrimack, Bayer, Symphogen, BioPharma, Genentech, Molecular Match, Symphogen, Guardant Health, EMD Serono, Merck. V. Zagonel: Advisory boards: Celgene, Bayer, Roche, Amgen, Novartis, Pfizer. J. Bennouna: Honoraria: Roche, Boehringer Ingelheim, Astrazeneca, Shire, MSD, BMS; consulting or advisory role: Roche, Boehringer Ingelheim, Astrazeneca, Shire, MSD, BMS. S. Siena: Advisory boards: Amgen, Roche, Bayer, Merck-Serono, Sanofi, Merrimack. A. Falcone: Advisory boards and research grants to Institution: Amgen, Merck, Roche, Bayer, Servier, Lilly, Sanofi. All other authors have declared no conflicts of interest.

**4790 Consensus molecular subtypes (cms) as predictors of benefit from bevacizumab in first line treatment of metastatic colorectal cancer: Retrospective analysis of the MAX clinical trial**

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**Background:** CMS is a transcriptome-based classification of colorectal cancer (CRC) with prognostic implications, but its association with treatment outcomes, especially in the metastatic setting, remains unknown. We investigated whether CMS classification was predictive of bevacizumab treatment benefit using data from the phase 3 MAX trial. MAX previously reported progression-free survival (PFS) benefit for the addition of bevacizumab (B) to chemotherapy (capcitabine (C)+/−mitomycin (M)) in first line treatment of metastatic CRC.

**Methods:** Archival tumours from 256 patients (54% of trial population) were available for gene expression profiling using Almac Xcel microarray. Tumours were classified for CMS as previously described. Tumours were classified for CMS in 3 or 4 subtypes using theanno map online tool (CancerCell) and retrospective analysis of the MAX clinical trial.

**Results:** After data quality control, primary tumours from 239 patients (51% of trial population) were suitable for survival analysis. Distribution of CMS groups were CMS1 18%, CMS2 48%, CMS3 12%, CMS4 23%. Hazard ratios (HR) (95% CI) of PFS in C vs B + CRM arms for CMS 1,2,3 and 4 were 0.83 (0.43-1.62), 0.50 (0.30-0.87), 0.51 (0.39-0.75) and 1.24 (0.68-2.25) respectively (test for interaction between CMS and treatment, p = 0.03). CMS remained a significant independent predictor of PFS after adjustment for prognostic factors in a multivariate analysis (p = 0.04).

**Table: 4780**

<table>
<thead>
<tr>
<th>Population</th>
<th>Arm A</th>
<th>Arm B</th>
<th>Arm C</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT N = 254</td>
<td>7.9* (6.5, 9.9) ²N = 83</td>
<td>10.3 (9.0, 12.9) N = 86</td>
<td>9.6 (8.3, 12.2) N = 85</td>
</tr>
<tr>
<td>US&amp;EU N = 224</td>
<td>7.7 (6.1, 13.3) N = 75</td>
<td>9.9 (8.0, 12.8) N = 74</td>
<td>8.5 (6.8, 10.2) N = 75</td>
</tr>
<tr>
<td>US&amp;EU with biomarker data N = 193</td>
<td>7.7 (5.5, 13.3) N = 70</td>
<td>9.9 (7.1, 12.9) N = 67</td>
<td>8.5 (6.4, 9.9) N = 56</td>
</tr>
<tr>
<td>US&amp;EU with DNNmCRC N = 170 (88%) ³N = 62</td>
<td>8.9 (6.2, 12.4) N = 62</td>
<td>11.9 (9.7, 13.8) N = 57</td>
<td>8.4 (6.4, 10.0) N = 51</td>
</tr>
<tr>
<td>US&amp;EU with TNNmCRC N = 131 (68%) ³N = 47</td>
<td>10.6 (6.8, 13.1) N = 47</td>
<td>12.8 (9.7, 14.7) N = 46</td>
<td>7.3 (6.3, 8.8) N = 38</td>
</tr>
</tbody>
</table>

*median survival in M
²95% confidence intervals
³the subgroup analyses excluded pts due to different medical practice
⁴with biomarker data
Conclusions: In metastatic CRC, CMS 2 and 3 subtypes preferentially benefit from the addition of bevacizumab to chemotherapy, compared to CMS 1 and 4. Validation of these findings in independent cohorts is required. Once validated, CMS classification could be used to guide patient selection for bevacizumab therapy.

Legal entity responsible for the study: Olivia Newton-John Cancer Research Institute, Australia

Funding: Olivia Newton-John Cancer Research Institute, Australia and Australian Gastrointestinal Trials Group (AGITG)

Disclosure: P. Laurent-Puig: Funding: Roche, Bayer and Sanofi for research in predictive biomarker for colorectal cancer. T. J. Price, N. Tebbutt: Advisory boards: Roche. Other authors have declared no conflicts of interest.

Background: While in the advanced setting right colon cancer is associated with a worse outcome, this negative prognostic effect has been not definitely demonstrated in the adjuvant setting. We have analyzed the outcome data from 3 large randomized trials (STITAC-1; SMAC and TOSCA) assessing adjuvant therapy in colon cancer patients with stage II and III. Furthermore, since previous trials were not powered to assess the prognostic role of transversal colon cancer, we analyzed this site independently.

Methods: In order to define the prognostic effect of right sidedness we assessed three randomized trials of adjuvant therapy (STITAC, SFUFA, vs control, 821 patients; SMAC, intraportal SFU vs SFUFA, 990 patients; TOSCA, FOLFOX or XELOX three vs six months 3513 patients) carried out in Italy from 1987 to 2013 and including 5324 patients.

Results: 5324 patients were included in this analysis, 2490 patients were males and 2834 females. Median age was 64 years. 2240 patients had a stage II colon cancer and 3084 a stage III. Right tumors were 1573 (30%), travesurus 822 (15%) and left 2929 (59%). Patients characteristics were well balanced among the three trials. In all the 5324 patients DFS was not affected by tumor location (right colon vs left, HR = 1.01, 95% CI = 0.89-1.15) while right tumor was associated to a worse OS compared to left tumor (HR = 1.21, 95% CI = 1.05-1.40) In stage II patients there was no difference in terms of DFS and OS among the three different tumor location while in stage III patients, right colon cancer had a worse outcome both in DFS and OS than left tumor (HR = 1.37, 95% CI = 1.16-1.64, p < 0.001).

Conclusions: This is the largest analysis demonstrating the prognostic effect of tumor location in colon cancer patients receiving adjuvant chemotherapy. The effect however is present only in stage III but not in stage II colon cancer.

Legal entity responsible for the study: GISCAD Foundation

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Background: Currently, robotic surgery for rectal cancer using da Vinci System is common. However, there is almost no clinical trial reported. This randomized controlled trial aims to compare the safety and efficacy of robotic-assisted, laparoscopic and open abdominopelvic resection (APR) for low rectal cancer.

Methods: From 2013-09 to 2017-03, patients aged from 18 to 75 years, with low rectal cancer within 5 cm from anal verge, clinical T1 to T3, no distant metastases, were randomly assigned to receive either robot-assisted procedures (RAP), laparoscopic procedures (LAP) or open surgery (OS) for APR in 1:1:1 ratio. The primary endpoint was postoperative complication rate.

Results: Totally 506 patients were enrolled in this study, randomly assigned to RAP (n = 169), LAP (n = 169), and OS (n = 168). Actually, 3 patients refused surgery, 173 finished RAP, 176 finished LAP, and 154 finished OS (including 4 convert from LAP to OS). The open conversion rate was 0 in RAP and 2.4% in LAP, with no significant difference (P = 0.125). In pre-procedure analysis, no significant difference was observed in tumor location, size, differentiation and pathological TNM stage, among the three groups. RAP had significantly lower postoperative complication rate (10.4%) than both LAP (18.8%, P = 0.027) and OS (26.6%, P < 0.001). Also, RAP reduced intraoperative hemorrhage (median, 100 ml) than LAP (130 ml, P < 0.001) and OS (200 ml, P < 0.001). And RAP promoted postoperative recovery, with shorter days to first flatus (2.6 days) than LAP (3.0 day, P < 0.001) and OS (3.3 days, P < 0.001), shorter days to first automatic urination (2.0 days) than LAP (3.0 days, P < 0.001) and OS (3.0 day, P < 0.001), and shorter days to discharge (5.0 days) than LAP (6.0 days, P < 0.001) and OS (6.0 day, P < 0.001). There was no significant difference in functional recovery. More details are shown in the table.

Conclusions: Robot-assisted APR was safe, and reproduce equivalent surgical quality of conventional laparoscopic and open surgery. Also, it provided less injury and faster functional recovery.
Results: 128 pts received CT and 129 CTX between Feb 2007 and Nov 2012. At a median follow-up of 69 months (IQR 59-81), 130 deaths (death from any cause) had been observed. Median OS was shorter for CTX vs CT (p = 0.001). There were numerically more multi-site progressions in CTX (n = 17/83, 20.5%) than CT (n = 8/78, 10.3%) pts and survival post-progression (PPS) was particularly poor for CTX pts (p = 0.014). Predefined subgroup analyses demonstrated the adverse effect of CTX was in pts conventionally thought to have good prognostic features. Whilst OS was the same for responders and non-responders on CT, it was improved for responders vs non-responders on CTX.

Conclusions: In the context of perioperative therapy for resectable CRLM CTX confers a shorter OS and survival post progression compared to CT. This detriment is in those with conventionally favourable prognostic features suggesting that cetuximab induces adverse biology in some pts, the biomarker profile of whom is being investigated. Response to CT alone does not improve OS compared to non-responders, suggesting conferred benefit is adjuvant not neoadjuvant.

Clinical trial identification: ISRCTN22944367

Legal entity responsible for the study: University Hospital Southampton NHS Foundation Trust

Funding: Cancer Research UK

Disclosure: J. Bridgewater: Honoraria and speakers fees: Merck, Celgene, Servier, Amgen; travel assistance Amgen, Merck Sharpe Dohme, Servier. T. Iverson: Consulting and/or advisory roles: Servier, Roche and Celgene; honoraria for services in the past two years: Lily; travel expenses: Bayer, Servier. J.W. Valle: Consultant/advisor: Ipsen, Novartis, AstraZeneca, Lilly, Merck, Baxalta, Delcath Systems, Agios, Pfizer, Midatech. Speakers’ bureau: Novartis, Pfizer, Celgene. Conducted research for his institution which have been funded, in whole or in part, by: Biotec, Roche. D. Cunningham: Has conducted research projects on behalf of his institution which have been funded, in whole or in part, by: Biotec, Roche. D. Cunningham: Has conducted research projects on behalf of his institution which have been funded, in whole or in part, by: Biotec, Roche. D. Cunningham: Has conducted research projects on behalf of his institution which have been funded, in whole or in part, by: Biotec, Roche. D. Cunningham: Has conducted research projects on behalf of his institution which have been funded, in whole or in part, by: Biotec, Roche. D. Cunningham: Has conducted research projects on behalf of his institution which have been funded, in whole or in part, by: Biotec, Roche.

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Background: In the CheckMate 142 trial (NCT02006188), NIVO + IPi demonstrated manageable safety and clinical activity characterized by an investigator-assessed objective response rate (ORR) of 21%, disease control rate (DCR) defined as CR + PR + SD (≥ 12 wk) of 79%, and encouraging survival benefit (6-mo PFS and OS rates: 77% and 89%) in pts with dMMR/MSI-H mCRC. Here, we report biomarker analyses in pts who received NIVO + IPi in the CheckMate 142 study.

Methods: Pts with dMMR/MSI-H mCRC who progressed on or after one line of treatment received NIVO 3 mg/kg + IFI 1 mg/kg Q2W. Tumor anti-programmed death ligand 1 (PD-L1) expression was assessed using the Dako 28-8 pharmDx assay. PD-L1 positivity was defined as ≥ 1% cell membrane staining of any intensity. BRAF and KRAS mutation statuses were determined by laboratories per local protocols. Characterization of Lynch syndrome as present or absent was based on past medical history from clinical records. ORR per investigator was determined per RECIST v1.1.

Results: Tumor PD-L1 expression and BRAF/KRAS statuses were assessed in 84 pts. ORR and DCR by BRAF/KRAS mutational status, and clinical history of Lynch syndrome are reported in the Table below.

Conclusions: Confirmed responses with NIVO + IPi were observed in pts with dMMR/MSI-H mCRC who were PD-L1 expressors and non-expressors, as well as across BRAF and KRAS mutational status. Responses were also observed in pts with or without a history of Lynch syndrome. These results are consistent with previously reported biomarker analyses of the NIVO monotherapy cohort.

Table: 484PD

<table>
<thead>
<tr>
<th>Pts, n (%)</th>
<th>[95%CI]</th>
<th>dMMR/MSI-H mCRC N = 84 Pts With ≥ 6 Mo of Follow-Up</th>
<th>ORR</th>
<th>DCR</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Pts, n (%)</th>
<th>[95%CI]</th>
<th>dMMR/MSI-H mCRC N = 84 Pts With ≥ 6 Mo of Follow-Up</th>
<th>ORR</th>
<th>DCR</th>
</tr>
</thead>
</table>

*18 pts had no quantifiable PD-L1 expression at baseline; **11 pts had unknown BRAF/KRAS status at baseline; ***52 pts had unknown Lynch syndrome status at baseline.


Legal entity responsible for the study: Bristol-Myers Squibb

Funding: Bristol-Myers Squibb

Disclosure: T. Andrea: Personal fees: Bristol-Myers Squibb, Roche, Servier, Baxter, Novartis, MSD, Amgen, Lilly, Sanofi, Hallidex, Xbotech and Boehringer Ingelheim. Non-financial support: Roche and BMS. M. Overman: Grants and personal fees from Bristol-Myers Squibb, outside the submitted work. S. Lonardi: Personal Fees: Amgen, Bayer, Lilly; Roche and Sanofi. M. Aglietta: Advisory board with BMS. R. McDermott: Personal fees: Clavis, Pfizer, and BMS; research funding from Merck, BMS, Janssen, and Bayer; grants from Piluso Exemgan and Amgen outside the submitted work. K.Y. Wang: Other from BMS, during the conduct of the study. M. Morse: Grants from BMS, during the conduct of the study. R.A. Moss: Employee and stock holder of BMS. J-M. Ledeine: Personal fees from Bristol-Myers Squibb, during the conduct of the study. H. Tang: Employee of BMS. Z.A. Cao: Employee of BMS and a stockholder of BMS and Novartis. S. Kopetz: Consulting/Advisor roles: Amgen, Array BioPharma, Bayer, BMS, Genentech, GSK, Janssen, Merrimack, MolecularMatch, Ocloose LLC, Roche, Sanofi, Sirtex Medical, Taiho Pharmaceutical Rich Funding-Agacana, Amgen, Biocartis, GSK, Guardant Health, Roche, Sanofi, Sysmex; other: MolecularMatch. All other authors have declared no conflicts of interest.

4860  Sequential first-line therapy of metastatic colorectal cancer (mCRC) starting with fluoropyrimidine (FP) plus bevacizumab (BEV) vs initial FP plus irinotecan (IRI) and BEV: German AIO KRK0110 (ML2011) study

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Background: The AIO KRK-0110 study compares a sequential application of FP + BEV followed by IRI + FP + BEV at first progression (arm A) vs initial FP + IRI + BEV (arm B) in patients (pts) with untreated mCRC.

Methods: The primary efficacy-endpoint was time-to-failure of strategy (TFS). The non-inferiority margin was a 9% confidence interval of a hazard ratio (HR) of 0.8 (Power 70%, α = 0.05). Secondary endpoints of the study included response rate, progression-free survival (PFS), overall survival (OS), efficacy in molecular subgroups and quality of life (EORTC QLQ C30).

Results: The full analysis set (FAS) consists of 421 pts (212/209 Arm A/B), median age was 71 years. The primary endpoint (TFS) was not met (HR: 0.86 (0.72-1.02)). Concerning TFS in patients with RAS/BRAF wild-type (WT) mCRC it appeared to have significant benefit from initial irinotecan while this was not observed in patients with mutant (MT) RAS/W or BRAF. A Cox model interaction test for study arm and RAS-status was significant (P = 0.03). PFS and OS were consistent with TFS (see table for details). Objective response rate favored the initial irinotecan-arm (36.8% vs 53.6%, P = 0.005). Quality of life (global health, physical functioning, etc.) was not substantially different between both study arms at baseline and end of treatment.

Conclusions: This trial in a particularly non-elderly population, non-inferiority for TFS of initial FP + BEV as compared to FP + IRI + BEV was not shown. In detail, sequential therapy was inferior in pts with RAS/BRAF-WT mCRC and cannot be recommended. However, sequential bevacizumab-based therapy could be discussed as an option in elderly pts with RAS MT mCRC. Conclusions on BRAF mutant tumors are limited by sample size.

Clinical trial identification: NCT01249638

Legal entity responsible for the study: Hospital of the University of Munich (LMU)

Funding: Roche


S. Benitez Majano, C. Di Giarolamo, M. Morris, B. Rachet, M.P. Coleman, S. Walters

Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK

Background: Colorectal cancer patients in England have worse outcomes than patients diagnosed in other high-income countries with similar healthcare coverage. We aim to compare clinical characteristics and survival of colorectal cancer patients in England, Norway and Sweden to understand whether differences in stage and treatment could help to explain international differences in survival.

Methods: Information on patients aged 15-99 years diagnosed with primary malignant tumours of the colon and rectum in England, Norway and Sweden during 2010-2012 was extracted from national cancer registration and/or specialised colorectal cancer registry data. Six-month, one-year and two-year net survival was estimated for each country, stage at diagnosis, and surgical treatment status.

Results: There were 93,125 colorectal cancer diagnoses in England, 11,155 in Norway, and 17,925 in Sweden during the time period. Stage was more advanced in colon than in rectal tumours. England had slightly poorer stage distribution, and a higher proportion of missing stage, than Norway and Sweden. Overall, 64.1% of colorectal cancer patients diagnosed in England, 68.8% diagnosed in Norway and 70.3% diagnosed in Sweden had evidence of receiving potentially curative surgery. These surgically treated patients were on average younger than those treated in Norway and Sweden, in each stage category. Stage-specific net survival was generally highest in patients in Sweden and lowest in those in England. The survival deficit of English patients was particularly large compared to similar patients in the other countries among those diagnosed with advanced disease and/or who did not receive potentially curative surgery.

Conclusions: Stage-specific survival from colorectal cancer in England was lower than in Norway and Sweden. This survival deficit may be partly explained by the higher proportion, and lower survival, of patients who did not receive potentially curative surgery in England. The different proportions of missing data may somewhat affect the comparability of the results however these remain informative.

Table: 486O

<table>
<thead>
<tr>
<th>Population</th>
<th>PFS-1</th>
<th>TFS</th>
<th>OS</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>mo. (95%)</td>
<td>Hazard ratio</td>
<td>P-value</td>
</tr>
<tr>
<td>FAS</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Arm A (N = 212)</td>
<td>8.0 (6.9-9.9)</td>
<td>0.70 (0.57-0.85)</td>
<td>P = 0.001</td>
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<td>Arm B (N = 209)</td>
<td>9.9 (8.7-10.9)</td>
<td>P &lt; 0.001</td>
<td>9.9 (8.8-10.6)</td>
</tr>
<tr>
<td>RAS/BRAF WT</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Arm A (N = 79)</td>
<td>8.4 (7.1-9.8)</td>
<td>0.49 (0.35-0.69)</td>
<td>P = 0.001</td>
</tr>
<tr>
<td>Arm B (N = 79)</td>
<td>12.6 (10.1-15.1)</td>
<td>P = 0.001</td>
<td>12.6 (10.4-14.3)</td>
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<td>RAS MT</td>
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<td></td>
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<td>Arm A (N = 91)</td>
<td>8.1 (6.0-10.2)</td>
<td>0.87 (0.65-1.17)</td>
<td>P = 0.03</td>
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<td>Arm B (N = 97)</td>
<td>9.3 (8.2-10.5)</td>
<td>P = 0.04</td>
<td>9.4 (8.0-10.7)</td>
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<td>BRAF MT</td>
<td></td>
<td></td>
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<tr>
<td>Arm A (N = 12)</td>
<td>5.8 (5.0-12.1)</td>
<td>1.43 (0.59-3.47)</td>
<td>P = 0.44</td>
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<tr>
<td>Arm B (N = 10)</td>
<td>4.5 (3.8-6.2)</td>
<td>P = 0.44</td>
<td>4.5 (3.1-8.4)</td>
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</table>
In this large cohort, early postoperative PET-CT changed the staging and management of up to 15% of pts with high-risk stage III CC and later reported also encouraging preliminary results in a larger cohort of consecutive pts with stage III CC, in which staging and management were altered in 14.9%. The aim of the current study was to expand the previous one to a larger cohort and to evaluate the actual impact of early postoperative PET-CT on pts outcome.

Methods: A Retrospective study of all consecutive pts with stage III CC who were treated at our institution and underwent early postoperative PET-CT between 2007-2009. Demographic and clinicopathological data were retrieved. Statistical analyses were done using standard methods.

Results: 348 pts, 166 (47.7%) males, with a median age of 66 years (range, 29-92), were included. Pathological stage was IIIA, IIB and IIC in 21.6%, 254 (73%) and 73 (21%) pts, respectively. The median number of lymph nodes assessed and examined and of positive ones were 14 (range, 3-54) and 2 (range, 0-32), respectively. High FDG uptake was noted in 95 (27.3%) pts, including 22 (6.6%) with clear postoperative changes and 18 (5.2%) pts, respectively. The median number of lymph nodes examined and of positive nodes included. Pathological stage was IIIA, IIIB and IIIC in 21(6%), 254 (73%) and 73 (21%) pts, respectively. The median number of lymph nodes examined and of positive ones included. Pathological stage was IIIA, IIIB and IIIC in 21(6%), 254 (73%) and 73 (21%) pts, respectively.

Conclusions: In this large cohort, early postoperative PET-CT changed the staging and management of 14.9% of pts with resected stage III CC, with encouraging outcome results.

Legal entity responsible for the study: Davidoff Cancer Center, Rabin Medical Center

Disclosure: All authors have declared no conflicts of interest.

Role of body composition in early stage colorectal cancer (CRC) outcomes

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Background: CRC is the 3rd most common cancer worldwide. Novel prognostic factors are needed to allow practitioners to stratify and personalize treatment and surveillance options to patients (pts). The objective of this study was to determine associations between body composition and disease-specific outcomes in early stage CRC.

We hypothesized that pts with sarcopenia or reduced muscle radiodensity (SMD) at time of surgery will have worse overall outcomes, specifically in their 5-year overall (OS) and disease free survival (DFS). Also, that pts with accelerated skeletal muscle loss at their 2-year surveillance computed tomography (CT) scan will have higher recurrence rates.

Methods: This is a retrospective cohort study of early stage (I-III) CRC from 2007-09. We excluded any pt without analyzable or preoperative CT scan or if a prior diagnosis of CRC. Routine CT imaging was used to measure skeletal muscle (SMA). Total body SMA was normalized for height (skeletal muscle index, SMI). An SMI <52.4 cm²/m² and <38.5 cm²/m² was used as a cutoff for sarcopenia in men and women, respectively. Mean muscle radiodensity in HU was obtained as a measure of myosteatosis.

Results: A total of 2049 pts were identified, of which 1455 had available, analyzable imaging. The report was 99% complete. The prevalence of sarcopenia was 45.9% in females and 56.2% in males, with an average SMI of 40 and 51 cm²/m², respectively. Average SMD was 31.5 HU for females and 33.2 HU for males. Pts with disease recurrence had a significantly lower SMI (49 ± 2 cm²/m², p < 0.001). Pts with recurrence also had lower HU (33.3 ± 30.3 HU, p = 0.001). The median time and average length of follow up was 5 yrs. Data collection and analysis is currently ongoing. We anticipate that pts with disease recurrence within 5 yrs of diagnosis will have a significantly faster rate of muscle loss.

Conclusions: Our study demonstrates for the first time body composition’s ability to predict recurrence of a solid tumor after curative treatment. Pts with reduced overall SMA and SMD had increased risks of disease recurrence. These findings if validated may allow better stratification of treatment and surveillance of CRC pts.

Legal entity responsible for the study: University of Alberta

Disclosure: Clinical Investigator Program - Alberta Health Flex

Funding: Clinical Investigator Program - Alberta Health Flex

All authors have declared no conflicts of interest.
Factors predicting adherence to a tailored-dose adjuvant treatment based on geriatric assessment in elderly people with colorectal cancer: A prospective study

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Background: Selecting elderly people with colorectal cancer (CRC) for adjuvant chemotherapy is challenging. Comprehensive geriatric assessment (CGA) can help by classifying them according to their frailty profile. The supposed benefit of chemotherapy is challenging. Comprehensive geriatric assessment (CGA) can help by adapting the dose to their frailty profile, and identifying adherence-related factors amenable to modification through CGA-based interventions.

Methods: Prospective study in 193 consecutive patients aged 75 or older. Based on CGA results, we classified patients as fit, medium-fit, or unfit, administering standard therapy, adjusted treatment and best supportive care, respectively. We recorded CGA results, we classified patients as fit, medium-fit, or unfit, administering standard therapy, adjusted treatment and best supportive care, respectively. We recorded

Results: Seventeen (13%) of the 141 candidates for chemotherapy (n = 86 fit and n = 55 medium-fit) refused treatment; associated factors included polypharmacy (odds ratio [OR] 5.61, CI95% 1.45, 21.49). Of the 105 patients receiving chemotherapy, 20 (27%) fit and 4 (13%) medium-fit patients experienced grade 3-4 toxicity (p = 0.11) without association to explanatory variables. About 55% of patients treated with chemotherapy received at least 80% of the planned dose (55% fit and 58% medium-fit patients; p = 0.7). Factors associated with completion of chemotherapy were the absence of toxicity (OR 7.67, CI95% 2.41, 24.43) and social support (OR 2.29, CI95% 0.08, 1.04).

Conclusions: CGA is useful for selecting elderly patients for adjuvant chemotherapy, adapting the dose to their frailty profile, and identifying adherence-related factors amenable to modification through CGA-based interventions.

Legal entity responsible for the study: Institut Català d’Oncologia

Funding: Fund for Health Research (FIS, PI 11/02011) and AGAUR (2014 SGR 0635)

Disclosure: All authors have declared no conflicts of interest.

Table: 491P

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Multivariate analysis</th>
<th>Treatment refusal n = 141</th>
<th>Toxicity grade ≥3 n = 105</th>
<th>Completion ≥80% of planned dose n = 105</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P-value</td>
<td>OR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td>Age</td>
<td>1.17 (0.95, 1.445)</td>
<td>0.15</td>
<td>3.21 (0.75, 13.79)</td>
<td>0.12</td>
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<tr>
<td>Sex</td>
<td>1.28 (0.51, 4.40)</td>
<td>0.33</td>
<td>1.26 (0.43, 3.65)</td>
<td>0.68</td>
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<tr>
<td>Cancer site Colon Rectum</td>
<td>1.17 (0.95, 1.445)</td>
<td>0.15</td>
<td>3.21 (0.75, 13.79)</td>
<td>0.12</td>
</tr>
<tr>
<td>Tumor stage II III</td>
<td>1.05 (0.17, 1.54)</td>
<td>0.23</td>
<td>5.34 (1.55, 18.40)</td>
<td>0.01</td>
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<tr>
<td>Polypharmacy</td>
<td>4.01 (3.999, 5.34)</td>
<td>&lt;0.001</td>
<td>1.71 (0.50, 5.92)</td>
<td>0.39</td>
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<tr>
<td>Weight loss &gt;10%/6 months</td>
<td>0.74 (0.20, 1.26)</td>
<td>0.80</td>
<td>0.48 (0.10, 2.37)</td>
<td>0.34</td>
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<td>Yesavage</td>
<td>1.20 (0.43, 3.40)</td>
<td>0.73</td>
<td>0.99 (0.40, 2.48)</td>
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<tr>
<td>Social support</td>
<td>5.78 (1.91, 17.47)</td>
<td>&lt;0.001</td>
<td>1.71 (0.50, 5.92)</td>
<td>0.39</td>
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<tr>
<td>VES-13 ≥3</td>
<td>1.341 (1.19, 9.777)</td>
<td>0.02</td>
<td>3.21 (0.75, 13.79)</td>
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<tr>
<td>Oncogeriatric group</td>
<td>1.286 (0.65, 12.50)</td>
<td>0.16</td>
<td>1.286 (0.65, 12.50)</td>
<td>0.16</td>
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Analysis (younger)

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Multivariate analysis</th>
<th>Treatment refusal n = 141</th>
<th>Toxicity grade ≥3 n = 105</th>
<th>Completion ≥80% of planned dose n = 105</th>
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<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P-value</td>
<td>OR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td>Age</td>
<td>2.72 (1.10, 6.72)</td>
<td>0.03</td>
<td>1.13 (0.95, 1.35)</td>
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<tr>
<td>Sex</td>
<td>2.12 (0.95, 4.78)</td>
<td>0.07</td>
<td>0.50 (0.20, 1.26)</td>
<td>0.14</td>
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<tr>
<td>Cancer site Colon Rectum</td>
<td>2.05 (0.34, 2.14)</td>
<td>0.73</td>
<td>0.50 (0.20, 1.26)</td>
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<tr>
<td>Tumor stage II III</td>
<td>1.085 (0.42, 2.72)</td>
<td>0.90</td>
<td>0.50 (0.20, 1.26)</td>
<td>0.09</td>
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<tr>
<td>Polypharmacy</td>
<td>2.31 (0.90, 5.95)</td>
<td>0.08</td>
<td>0.50 (0.20, 1.26)</td>
<td>0.09</td>
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<tr>
<td>Weight loss &gt;10%/6 months</td>
<td>1.09 (0.37, 3.27)</td>
<td>0.87</td>
<td>0.50 (0.20, 1.26)</td>
<td>0.09</td>
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<tr>
<td>Yesavage</td>
<td>1.08 (0.50, 2.34)</td>
<td>0.85</td>
<td>0.50 (0.20, 1.26)</td>
<td>0.09</td>
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<tr>
<td>Social support</td>
<td>3.24 (0.10, 10.11)</td>
<td>0.04</td>
<td>0.50 (0.20, 1.26)</td>
<td>0.09</td>
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<tr>
<td>VES-13 ≥3</td>
<td>0.92 (0.29, 2.85)</td>
<td>0.88</td>
<td>0.50 (0.20, 1.26)</td>
<td>0.09</td>
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<tr>
<td>Oncogeriatric group</td>
<td>0.85 (0.36, 1.98)</td>
<td>0.71</td>
<td>0.50 (0.20, 1.26)</td>
<td>0.09</td>
</tr>
<tr>
<td>Toxicity</td>
<td>7.19 (2.45, 21.32)</td>
<td>&lt;0.001</td>
<td>0.13 (0.04,0.42)</td>
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Background: UPTR remains controversial in the initial management of unresectable asymptomatic mCRC patients (pts), whereas right sidedness is a bad prognostic factor.

Methods: Retrospective pooled analysis of KRAS WT mCRC pts treated with 1st line EGFR inhibitors (EGFRi) + chemotherapy (CT) from two phase II randomised trials (MACRO-2 & PLANET). We analysed UPTR effect on overall survival (OS) and progression free survival (PFS) by tumour sidedness (right/left) and stage (I-III/IV) at diagnosis. All stage I-III pts underwent UPTR at diagnosis as standard procedure.

Results: 260 pts were included in the analysis (Table). In pts with stage IV at diagnosis, UPTR was associated with a better OS, although differences were only significant in right sided tumours (mOS (m): 20.9 vs 10.6; HR non-UPTR vs UPTR 2.1 (1.0, 4.3); p 0.036). Conversely, left sided tumours had a significantly better OS vs right sided tumours regardless of UPTR: UPTR HR 0.4 (0.2, 0.8); p 0.006; no UPTR HR 0.2 (0.1, 0.4); p <0.0001. In pts with stage I-III at diagnosis (all UPTR), there were no differences in OS according to sidedness. After UPTR, OS was significantly higher in stage I-III tumours vs stage IV only in right sided tumours. Similar results were observed for PFS.

Conclusions: In mCRC KRAS WT pts treated in 1st line with EGFRi + CT, UPTR seemed to improve outcomes particularly in right sided tumours. Table: 492P Median (95%CI) OS and PFS

<table>
<thead>
<tr>
<th>Table: 492P</th>
<th>Right</th>
<th>Left</th>
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</thead>
<tbody>
<tr>
<td><strong>Stage I-III at diagnosis</strong></td>
<td></td>
<td></td>
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<tr>
<td>N</td>
<td>9</td>
<td>31</td>
</tr>
<tr>
<td>OS(m)</td>
<td>34.9</td>
<td>28.9</td>
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<tr>
<td>(10.6 - )</td>
<td>(17.6 - )</td>
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<tr>
<td>HR left vs right</td>
<td>1.5 (0.6, 4.1)</td>
<td>p</td>
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<tr>
<td><strong>PFS(m)</strong></td>
<td></td>
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<tr>
<td>14.3</td>
<td>10.8</td>
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<tr>
<td>(8.5, 19.8)</td>
<td>(7.6, 13.9)</td>
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<tr>
<td>HR left vs right</td>
<td>1.7 (0.7, 4.2)</td>
<td>p</td>
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<tr>
<td><strong>Stage IV at diagnosis</strong></td>
<td></td>
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</tr>
<tr>
<td>N</td>
<td>18</td>
<td>24</td>
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<tr>
<td>OS(m)</td>
<td>20.9</td>
<td>10.6</td>
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<tr>
<td>(5.9, 34.2)</td>
<td>(6.3, 11.8)</td>
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</tr>
<tr>
<td>HR No UPTR vs UPTR</td>
<td>2.1 (1.0, 4.3)</td>
<td>p</td>
</tr>
<tr>
<td><strong>UPTR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR left vs right</td>
<td>0.4 (0.2, 0.8)</td>
<td>p</td>
</tr>
<tr>
<td>HR Stage IV vs Stage III</td>
<td>4.4 (1.4, 13.9)</td>
<td>p</td>
</tr>
</tbody>
</table>

Continued
Conclusions: These exploratory analyses suggest the technical aspects of surgery are similar between the treatment groups and that those patients having smaller volume resections may be disadvantaged by the addition of cetuximab.

Clinical trial identification: ISRCTN 22944367

Legal entity responsible for the study: University Hospital Southampton NHS Foundation Trust

Funding: Cancer Research UK

Disclosure: D. O’Reilly: Received expenses, travel, accommodation or otherwise, from AngioDynamics and Mylan. M. Peterson: Received expenses, travel, accommodation or otherwise, from Telixel. N. Heath: Has provided and been paid, including honoraria, for consulting and/or advisory roles and participating in a speakers’ bureau by Astellas. Has a patent or other royalties/ intellectual property under his own account. G. Griffiths: Has provided and been paid for consulting and/or advisory roles for the following companies: AstraZeneca, Bayer, Celgene, Merrimack, MedImmune, Merck Serono and Sanofi. T. Maughan: Has provided and been paid for consulting and/or advisory roles for the following company in the past two years: Vertex. J. Garden: Participated in a speakers’ bureau for a Johnson and Johnson (Edison) workshop (May 2016). All other authors have declared no conflicts of interest.

495P Prognostic impact of tumor deposits in colorectal cancer with lymph nodes metastasis

F. Liu 1, Zhao 1, Yang 1, Xu
Department of Colorectal Surgery, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Tumor deposit (TD) was an important clinical characteristic associated with adverse prognosis in colorectal cancer (CRC), reported in 4.9%–41.8% CRC patients. The frequent alteration of TDs definition and category in the recent 4 versions of TNM staging system make it controversial. There are several points that are not clear in the latest TNM classification regarding the coexistence of TDs and LNM and the comparison of the prognosis value between TDs and LNMs.

Methods: Two large-scale cohorts were collected for optimally categorizing TDs with LNM in the tumor stage. The first cohort was from the SEER database involving 65,537 patients between 2011 and 2013. The second cohort was from Fudan University Shanghai Cancer Center (FUSCC) involving 2837 patients between 2010 and 2014.

Results: TDs were observed in 6.3% of patients in SEER cohort and 14.7% in FUSCC cohort. A significantly reduced overall survival was observed for TDs in LNM positive CRC patients (hazard ratio [HR], 1.65; 95% CI, 1.54 to 1.76) in SEER cohort. Prognosis became worse as the number of LNMs increasing, but there was no significant difference in different numbers of TDs in the SEER cohort and FUSCC cohort. Therefore, whether TDs exist or not was the main point. Further analysis combining TDs with LNM shows that there is no significant difference in terms of the impact on overall survival between N1 and N1c, between N1 with TDs (NDT2) and N2. The 3-year survival rate was 82.3%, 72.0%, 69.9%, 55.7%, 52.1%, 39.4% for N0, N1, N1c, N1TD, N2 and N2 with TDs (NDT2) respectively in SEER cohort. Similar results were observed in the FUSCC cohort.

Conclusions: TD should not be considered as LNM, because they have different survival impact based on our study results. TDs and LNMs could be integrated into a modified pathological N category: including N0 (N0), N1c (N1), N1TD (N2) and N2TD. Among these subtypes, the prediction of Nigic and N1 was similar which means that the revision concerning TDs in the 7th TNM staging system is adequate to predict the pNcic patients’ outcome. For the condition of TDs and LNM coexistence, the prognosis of N2TD was the worst. Therefore, the modified pathological N category was reasonable solution to apply TDs into the pN category of TNM staging system.

Legal entity responsible for the study: Fudan University Shanghai Cancer Center

Funding: National Natural Science Foundation of China (No. 81472620) and Shanghai Science Foundation of China (No. 16ZR1406700)

Disclosure: All authors have declared no conflicts of interest.

496P Predictive potential of tumour-stroma ratio on benefit from adjuvant bevacizumab in high-risk stage II and stage III colon cancer

S. Zuderer 1, G. van Petel 1, H. Geldenslom 1, R. Tollenraaij 1, C. Marcano 2, W. Mesker 1

1Surgery, Leiden University Medical Center (LUMC), Leiden, Netherlands
2Medical Oncology, Leiden University Medical Center (LUMC), Leiden, Netherlands
3Genentech, F. Hoffmann-La Roche AG, Basel, Switzerland

Background: The tumour-stroma ratio (TSR) has proven to be an independent prognostic factor in colon cancer. We evaluated the predictive potential of TSR on disease free survival (DFS) and overall survival (OS) in patients with high-risk stage II and stage III colon cancer who received standard oxaliplatin-based chemotherapy with or without bevacizumab.

Methods: Haematoyxin and Eosin stained tumour slides of 1212 patients (42% of intention-to-treat [ITT]) enrolled in the AVANT trial were microscopically scored for TSR and categorized as stroma-low or stroma-high. TSR scores were correlated to the primary endpoint DFS and secondary endpoint OS.

Results: Of 1212 tumour slides, 1163 could be scored for TSR. Patients with stroma-high tumours (n = 339) had a significant shorter DFS (p = 0.001) compared to patients with stroma-low tumours (n = 824). In the AVANT trial addition of bevacizumab did not prolong DFS and data suggested a potential detrimental effect on OS. In our study, the bevacizumab – FOLOFOX-4 arm had a significantly shorter DFS compared to FOLOFOX-4 in stroma-low tumours, with a hazard ratio (HR) of 1.94 (95% CI 1.24 – 3.04; p = 0.004). However, in stroma-high tumours the effect was reversed and showed a trend for better DFS when adding bevacizumab to FOLOFOX-4 versus FOLOFOX-4 (HR 0.61; 95% CI 0.35 – 1.07; p = 0.08). For bevacizumab- XELOX versus FOLOFOX-4, this was not seen (stroma-low HR 1.07 (95% CI 0.64-1.77; p = 0.80); stroma-high HR 0.78 (95% CI 0.47-1.30; p = 0.55)). For OS the same pattern was observed for bevacizumab: FOLOFOX-4 versus FOLOFOX-4 with a HR of 2.53 (95% CI 1.36-4.71; p = 0.003) for stroma-low and HR 1.95 (95% CI 0.32-1.14; p = 0.01) for stroma-high tumours. For bevacizumab – XELOX versus FOLOFOX-4, this was 1.13 (95% CI 0.55-2.31; p = 0.74) for stroma-low tumours and HR 0.74 (95% CI 0.37-1.51; p = 0.43) for stroma-high tumours.

Conclusions: Addition of bevacizumab to intravenous oxaliplatin-based chemotherapy suggests, in accordance with AVANT ITT analysis, a pronounced shorter DFS and OS in low stromal tumours. In contrast, in high stromal tumours a (potential) beneficial trend is observed when adding bevacizumab to intravenous oxaliplatin-based chemotherapy.
Tumor-stroma interactions and response to targeted agents in preclinical models of colorectal cancer (CRC)

C. Bazzichetto, F. Concari, I. Falcone, F. Cognetti, L. Coiffreda, M. Milella
Medical Oncology 1, Regina Elena National Cancer Institute, Rome, Italy

Background: Recent evidence suggests that genetically “normal” tumor microenvironment may react to pathway inhibitors by upregulating signaling pathways and modulating the sensitivity of cancer cells to targeted agents. The aim of this study was to uncover the mechanisms by which stromal cells modulate the sensitivity of tumor cells in response to signaling inhibitors.

Methods: We monitored the functional effects of MEK and PI3K/mTOR inhibitors (trametinib/gedatolisib) on isogenic CRC cell lines (HCT116 and HCT116 PTEN<sup>-/-</sup>) in the presence or absence of stromal fibroblasts or fibroblast/endothelial cell conditioned medium (CM); moreover, we evaluated pathway activation under different culture conditions and analysed the cytokine/chemokine profile.

Results: Trametinib/gedatolisib combinations were additive in HCT116 (combination index, CI = 1) and strongly synergistic in HCT116 PTEN<sup>-/-</sup> (CI = 0.25). Under conditions of direct cell-cell contact, co-culture with HCT116 PTEN<sup>-/-</sup> rendered fibroblasts hypersensitive to combined trametinib/gedatolisib combinations, while co-culture with HCT116 actually protected the stromal component. CM from different types of stromal cells (fibroblasts: HFF, HE, BJ; endothelial cells: EA-hy926) differentially affected the response of HCT116 (but not HCT116 PTEN<sup>-/-</sup>) to signaling inhibitors: in particular, HFF- and EA-hy926-CM rendered HCT116 hypersensitive to PI3K/mTOR blockade by single-agent gedatolisib moreover, EA-hy926 rendered HCT116 PTEN<sup>-/-</sup> more sensitive to trametinib. Pathway activation analysis showed more prominent downregulation of Akt phosphorylation in response to PI3K/mTOR inhibition in the presence of fibroblast-conditioned medium. Angiogenesis microarrays demonstrated a diversified profile of cytokine/chemokine production in stromal cells from different sources, particularly in terms of IL-6, IL-8 and MCP-1 production.

Conclusions: Stromal cells differentially affected response of CRC to agents targeting the MAPK and PI3K pathways; such effects varied depending on the genetic background of the tumor cell (PTEN-competent or PTEN-los) and on the modality of tumor stroma interaction (direct cell contact or soluble factors).

Legal entity responsible for the study: Wilma Mesker, assistant professor LUMC

Disclosure: All authors have declared no conflicts of interest.
Results: There were no significant differences in patient background characteristics, except for age and pathological T stage, between the LLND and without-LLND groups. Younger patients were often selected as candidates for LLND, and LLND had no impact on RFS or overall survival (OS) in all patients with lower rectal cancer (hazard ratio [HR] = 0.941, 95% confidence interval [CI]: 0.869–1.271). In Stage III/IVC patients, LLND improved the RFS (HR = 0.786, 95% CI: 0.489–1.260) and UFT arms (HR = 0.790, 95% CI: 0.497–1.283), despite the better RFS in the 5-FU arm than in the UFT arm. LLND did not show a major impact on OS in Stage III/IVC patients.

Conclusions: This exploratory analysis showed that LLND improves RFS in patients receiving either 5-FU or 5-FU therapy, although the results were not significant. LLND has an additional impact on improving RFS of patients with lower rectal cancer undergoing adjuvant chemotherapy.

Clinical trial identification: UMIN-CTR (C00000385)

Legal entity responsible for the study: Japanese foundation for multidisciplinary treatment of cancer

Funding: None

Disclosure: E. Oki: Honoraria for lecturing from Taiho Pharmaceutical Co., Ltd.; Yakult Honsha Co., Ltd.; and Chugai Pharmaceutical Co., Ltd., All other authors have declared no conflicts of interest.

SOP2 Effects of mesorectal fascia (MRF) status for locally advanced rectal cancer: Results of a multicenter, randomized, controlled, phase II trial (FORD-007)

J. Zhu, C. Li
Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

Background: To identify the effects of high-dose intensity modulated radiation therapy (IMRT) for locally advanced rectal cancer according to MRF status.

Methods: Eligible patients from multicenter who had histologically confirmed locally advanced rectal adenocarcinoma (cT3-T4 and/or cN+) located within 12 cm from the anal verge, were randomly assigned (1:1) to either the low intensity group (50 Gy/25FxS concurrent with capecitabine 500 mg/m² weekly and capecitabine 625 mg/m² bid di 1–5 weekly) or the high intensity group (50 Gy/25FxS and a concomitant boost of 5 Gy to the primary tumor, followed by one cycle of XELOX two weeks after the completion of chemoradiotherapy). Surgery was scheduled eight weeks after the completion of CRT. All patients were recommended to receive postoperative XELOX chemotherapy regardless of pathological stage. The primary endpoint was pathological complete response rate (pCR). Secondary endpoints included LC, OS, DFS and toxicities.

Results: From February 2010 to December 2011, 120 locally advanced rectal cancer patients (60 in high intensity group and 60 in low intensity group) were involved. The data were analyzed by MRF status (74 in the MRF- group and 46 in the MRF+ group). Patients in the MRF- group had better pCR (21.6% vs. 13.0%, p = 0.238), LC (p = 0.012), DFS (p = 0.002) and OS (p = 0.007) than those in MRF+ group. While stratified with MRF status, high intensity group showed a better tumor response, especially in MRF+ group. But no significant interaction between MRF and intensity was found in long-term prognosis.

Conclusions: MRF is a strong prognostic factor and a predictor of tumor regression. High-dose treatment may be beneficial to MRF+ patients via improving tumor response.

Clinical trial identification: NCT01064999

Legal entity responsible for the study: Department of Radiation Oncology, Fudan University Shanghai Cancer Center

Funding: None

Disclosure: All authors have declared no conflicts of interest.

SOP3 Planned organ preservation for selected T2, T3 rectal cancer: French experience using chemo radiotherapy and contact X ray boost

J-P. Gérard1, N. Barber2, K. Benezery-Sanná3, R. Coquard4, Y. Chateau5, J. Gal2, J. Doyen3
1Radiothérapie, Centre Antoine Lacassagne, Nice, France, 2Radiothérapie, Centre de Radiothérapie, Marsen, France, 3Radiothérapie, Centre Antoine Lacassagne, Nice, France, 4Radiothérapie, Centre Bayard, Lyon Villeurbanne, France, 5Research Department, Centre Antoine Lacassagne, Nice, France

Background: Combining CRT (50 Gy + capecitabine) and CXB boost provides high probability of organ preservation. We report the experience of three French institutions using CXB.

Methods: Selection used digital rectal examination, colonoscopy, MRI (and/ or Endorectal-ultrasound, 18FDG Pet-CT). Inclusion was: adenocarcinoma (distal, mid- rectum), T2 T3a-b, tumor diameter ≤ 4 cm, N0, M0. Treatment: CXB (80-110 Gy/ 3-4 F) followed by CRT (CAP 50). Tumor response assessed on week 14 after start of treatment using digital rectidend scopy and MRI. Clinical complete response (cCR) was defined as no visible tumor, supple rectal wall and TRG 1-2 MRI. In case of cCR a close surveillance or local excision was proposed.

Results: Between 2002 -2016, 84 patients were treated (Lyonvilleurbanne: 16, Mâcon: 11, Nice: 57). Median age: 73 years, Male: 59, Female: 25. T2:52; T3:32. Operable patients: 69 (83%). Median follow-up time was 53 months. A cCR was achieved in 94% of cases. Local excision was performed in 16 patients (yptp(3)1:14). At 4 years, the cancer specific survival was 82% (CI 96-70%) and the local relapse rate 12% (CI 2-22%). 7 local relapses were seen with 2 patients with 5 years with one isolated perirectal lymph node relapse at 7 years. Acute grade 3 toxicity (diarrhea, proctitis) was seen in 9 patients mainly related to CRT and did not require treatment modification. Main late toxicity (> 6 months after treatment) was rectal bleeding (due to radiation telangiectasia) which required plasma group organ coagulation in 5 patients. No TME surgery was performed and organ preservation was achieved in all cases (75 patients with local control). Bowel function was good (LARS score> 20) in 85% of patients with no diverting stoma for poor function.

Conclusions: After adequate selection and treatment, rectal cancer T2T3a-b N0 ≤4cm can achieve a high rate of cCR (>85%) with organ preservation, good bowel function and low rate of local relapse (< 15%) with low toxicity. Prolonged follow-up is mandatory. As rectal adenocarcinoma is radiosensitive tumor, the treatment must combine CRT and CXB boost. Like anal squamous cell cancer, planned organ preservation can be proposed to operable patients. The ongoing European OPERA trial aims at bringing evidence to this option.


Legal entity responsible for the study: Centre Antoine Lacassagne, Nice, France

Funding: None

Disclosure: J.-P. Gérard: Medical advisor of Ariane Medical system company Derbi, UK. All other authors have declared no conflicts of interest.
Optimal therapeutic strategy in patients (pts) with RCSM remains a matter of debate.

Chemotherapy-naive pts with RCSM received FOLFIRINOX: oxaliplatin 85 mg/m² d1, irinotecan 180 mg/m² d1, leucovorin 400 mg/m² d1 followed by FU 400 mg/m² bolus d1 and 2, 400 mg/m² 46h continuous infusion biweekly; 8 cycles were planned. The 4m DC was 94% (95% CI, 86.3-97.8).

Background: Optimal therapeutic strategy in patients (pts) with RCSM remains discussed and many front-line options can be discussed to best treat primary tumor and metastatic disease: surgery (S), radiotherapy (RT), chemoradiotherapy (CRT) or chemotherapy (CT). The FFCD 1102 trial evaluated the efficacy of upfront FOLFIRINOX in this setting.

Methods: Chemotherapy-naive pts with RCSM received FOLFIRINOX: oxaliplatin 85 mg/m² d1, irinotecan 180 mg/m² d1, leucovorin 400 mg/m² d1 followed by FU 400 mg/m² bolus d1 and 2, 400 mg/m² 46h continuous infusion biweekly; 8 cycles were mandatory. CT-scan and MRI at baseline, 2 and 4 months (m) were centrally reviewed. The pCR rates were assessed on CT-scan for metastases (RECIST criteria) and MRI for rectal tumor (volume decrease ≥70%). The primary endpoint was disease control rate at 4 m (4m DC). With a Simon 2-stage design, a targeted (H1) 4m DC >75% was defined (unilateral alpha of 5% and statistical power of 90%).

Results: 65 pts were enrolled (07/2012 to 02/2015): male 78%, median age 61 years; PS 0-1 99%, liver metastases 92%; 2 metastatic sites 63%. All pts received at least 1 cycle of CT, and 85% the 8 planned cycles. The 4m DC was 94% (95% CI, 86.3-97.8).

Conclusion: FOLFIRINOX is active in patients with locally advanced rectal cancer, allowing a local and distal control of RCSM, and leaves the opportunity to decide best therapeutic strategy according to the response obtained after the induction step.

Legal entity responsible for the study: FFCD (Fédération Francophone de Cancérologie Digestive)

Funding: FFCD (Fédération Francophone de Cancérologie Digestive)

Disclosure: J. Bachet: Honoraria: Bayer, Cegenole, Sanofi; consulting or advisory role: Amgen, Bayer, Merck Serono, Servier; travel, accommodation: Amgen, Cegenole, Sanofi; pharmaceutical research funding: Bayer, Cegenole, Sanofi; travel, accommodation: Amgen, Cegenole, Sanofi; research funding: Bayer, Gilead, Merck-Serono, Novartis, AstraZeneca.

506P Neoadjuvant treatment with mFOLFOXIRI alone versus chemoradiotherapy in locally advanced rectal cancer: A propensity score analysis from two prospective trials

J. Zhang1, Y. Cai1, H. Hu1, D. Chen1, J. Xiao1, W. Wang1, P. Lam1, M. Huang1, L. Wang2, X. Wu1, J. Kang1, J. Wang1, Y. Deng1

1Medical Oncology, The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; 2Surgical Oncology, The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

Background: Neoadjuvant chemoradiotherapy (CRT) is the standard of treatment for locally advanced rectal cancer, but it delays administration of systemic chemotherapy, leading to high incidence of distant metastases. To enhance systemic chemotherapy and avoid the delay of radiation, neoadjuvant chemotherapy regimens were under investigation. Here, we aimed to compare the efficacy of neoadjuvant chemoradiotherapy with mFOLFOXIRI alone versus chemoradiotherapy in locally advanced rectal cancer.

Methods: Prospectively maintained databases of patients from two clinical trials (NCT01211210 and NCT02217020) underwent neoadjuvant treatment for locally advanced rectal cancer in a single center were included. Those had received standard CRT or mFOLFOXIRI chemotherapy alone preoperatively were selected for this study. All patients had undergone total mesorectal excision. A comparative analysis was performed after the implementation of propensity score matching on the 2 main cohorts (mFOLFOXIRI and CRT).

Results: A total of 142 patients were included in the study, with median age of 51 years old. By propensity score matching, 71 patients were comparable in the two groups. Comparable pathologic complete response (pCR) rate (15.3% vs. 12.7%, P = 0.63) and tumor downstaging rate (42.3% vs. 36.6%, P = 0.49) were observed in the mFOLFOXIRI group and CRT group, respectively. The anal preservation rate was similar between the two groups (87.3% vs. 88.7%, P = 0.79). But lower incidence of anastomotic fistula (7.0% vs. 19.7%, P = 0.026) was shown in mFOLFOXIRI alone group than that of CRT group. And radiation-related dermatitis or proctitis was occurred in 41.7% of patients in the CRT group.

Conclusion: Neoadjuvant mFOLFOXIRI chemotherapy alone showed similar early efficacy in terms of pCR rate and tumor downstaging rate when comparing with CRT, and led to less toxicity and fewer postoperative complications. But this finding requires further analysis from long-term survival data. The phase III study comparing FOLFOXIRI with CRT is ongoing.

Clinical trial identification: This study included two prospective clinical trials NCT01211210 (FOWARC study) and NCT02217020 (FORTUNE study).

Legal entity responsible for the study: Yanhong Deng

Funding: None

Disclosure: All authors have declared no conflicts of interest.

507P Updated survival results of FACT trial: Multicenter phase II trial of neoadjuvant chemotherapy with mFOLFOX6 for stage II/III rectal cancer with a 3/4 tumor

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Background: The multicenter phase II FACT trial demonstrated that modified FOLFOX6 (mFOLFOX6) was efficacious treatment for stage II/III rectal cancer patients with a T3/4 tumor (Koike J, et al. Cancer Chemother Pharmacol 2017). We now reported the disease-free survival (DFS) and overall survival (OS) after a median follow-up of more than 3 years.

Methods: Patients received four 2-week cycles of mFOLFOX6 therapy (oxaliplatin at 85 mg/m² + leucovorin at 200 mg/m² + fluorouracil as a 400 mg/m² bolus followed by infusion of 2,400 mg/m² over 46 hours, all on Day 1). They were evaluated by...
computed tomography after completion of the fourth cycle. If there was no disease progression, two additional cycles were administered and then surgery was performed. Adjuvant chemotherapy was generally administered for 6 months using various regimens at the discretion of the physician.

Results: At a median follow-up of 42.8 months, median DFS from registration of clinical trials was 42.2 months, and median DFS from surgery was 38.9 months. Median survival time (MST) from registration of clinical trials was 42.8 months, and OS from surgery was 38.9 months. The safety profile was almost similar to previous analysis results.

Conclusions: Neoadjuvant chemotherapy using mOFLX/r8 for stage II/III rectal cancer patients with a T3/T4 tumor was well tolerated, as previously reported. In this trial, neoadjuvant mOFLX/r8 showed improved median DFS and MST.

Legal entity responsible for the study: FACT trial group

Funding: None

Disclosure: All authors have declared no conflicts of interest.

**SO8P**

Phase II randomized trial of capecitabine + radiation therapy with/without bevacizumab as preoperative treatment for patients with resectable locally advanced rectal adenocarcinoma: Final results of 3 and 5-year disease free survival, distant relapse free survival and overall survival

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Background: Combined modality treatment with preoperative radiation therapy (RT) + capecitabine is a standard of care for locally advanced rectal adenocarcinoma. However, new strategies to improve outcomes are necessary. We previously reported neither difference in pathologic complete response (primary objective) nor in safety results with preoperative RT + capecitabine with or without Bev. We present now the Disease-free survival (DFS), distant relapse free survival (RFS) and Overall Survival (OS) data at 3 and 5 years.

Methods: Patients (pts) were randomized in a 1:1 ratio to 5 weeks (w) of RT 45 Gy with capecitabine with or without Bev. We present now the results of 3 and 5-year DFS, RFS and OS. DFS is defined as time from randomization to the first documented disease progression. Patients were stratified by clinicopathological characteristics (Mandard TRG, pathological type, differentiation degree) before randomization. We compared between long-course (42 Gy) and short-course (34 Gy) RT, respectively.

Results: Ninety pts were included (44 in arm A and 46 in arm B). Preoperative treatment compliance was similar in both arms. Seventy-five pts received adjuvant systemic chemotherapy: 34 (77.3%) in arm A and 41 (89.1%) in arm B (p = 0.131). One pt (arm B) developed local relapse. Eleven pts in arm A and 13 in arm B developed distant metastasis. With a median follow-up of 63.5 and 63.5 months for arms A and B, respectively, median DFS, median RFS and median OS have not been reached for both arms. OS at 3 and 5 years was 80.4% and 78.3% (arm B), respectively (5y-distant RFS, p = 0.9820). Distant RFS at 3 y and 5 y was 80.4% and 78.3% (arm B), respectively (5y-distant RFS, p = 0.9820). Distant RFS at 3 y and 5 y was 80.4% and 78.3% (arm B), respectively (5y-distant RFS, p = 0.9820). Distant RFS at 3 y and 5 y was 80.4% and 78.3% (arm B), respectively (5y-distant RFS, p = 0.9820). Distant RFS at 3 y and 5 y was 80.4% and 78.3% (arm B), respectively (5y-distant RFS, p = 0.9820). Distant RFS at 3 y and 5 y was 80.4% and 78.3% (arm B), respectively (5y-distant RFS, p = 0.9820). Distant RFS at 3 y and 5 y was 80.4% and 78.3% (arm B), respectively (5y-distant RFS, p = 0.9820). Distant RFS at 3 y and 5 y was 80.4% and 78.3% (arm B), respectively (5y-distant RFS, p = 0.9820).

Conclusions: In our study, the addition of bevacizumab to capecitabine and radiotherapy in the neoadjuvant setting for locally advanced rectal cancer does not confer benefits in DFS, RFS or OS.

Clinical trial identification: NCT01405844

Legal entity responsible for the study: The Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD)

Funding: Roche

Disclosure: All authors have declared no conflicts of interest.
Background: Patients with liver metastases from colorectal cancer are in 80% of cases non-resected for resection. The standard first line treatment of unresectable liver metastases is systemic chemotherapy; however, this method results in progression for 70% of patients. The indicated therapy for refractory patients is the chemoembolization. In this study we monitored tumor response and adverse events after chemoembolization of colorectal cancer liver metastases with polyethylene glycol embolics loaded with irinotecan. Secondary objectives were to monitor quality of life, time to progression and survival of patients.

Methods: Patients were included in the study if affected by CRC-LM, who were refractory to systemic therapy, treated with chemoembolization using polyethylene glycol embolics, and liver involvement >50%. Tumor response, performance status (PS), tumor marker antigens, and quality of life (QoL) were monitored at 1, 3 and 6 months after chemoembolization. QoL was assessed with the palliative scale (PS8).

Results: We treated 30 consecutive CRC-LM patients with chemoembolization using polyethylene glycol embolics, their tumor response one month after chemoembolization was 28% of complete response (CR), and 48% of partial response (PR), 8% stable disease (SD), and 16% of progression. Tumor response 3 months after chemoembolization was CR 24%, PR 38%, SD 19% and progression disease (PD) 19%. Tumor response 6 months after chemoembolization was CR 18%, PR 44%, SD 21% and progression disease (PD) 18%. QoL was 90% PPS at each point time. Median time to progression was 2.5 months (range 0.8-6). Median follow-up was 14 months (0.8-25 range). Chemoembolizations were performed with no complications. Observed side effects (mild or moderate intensity) were: pain in 32% of patients, increase of transaminase levels in 20% liver in 14%, whereas 30% of patients did not complain any adverse event.

Conclusions: Chemoembolization of refractory liver metastases from colorectal cancer with polyethylene glycol embolics loaded with irinotecan was effective in tumor regression and resulted in mild toxicity, and good QoL.

Clinical trial identification: NCT01891552

Legal entity responsible for the study: Giammaria Fiorentini

Funding: None

Disclosure: All authors have declared no conflicts of interest.

512P Neoadjuvant systemic chemotherapy prior to cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for the treatment of peritoneal carcinomatosis from colorectal cancer

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Background: Cytoreductive surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) have become a standard treatment option for peritoneal carcinomatosis (PC) arising from colorectal carcinoma, despite the complexity and morbidity of this procedure. The timing of CRS+HIPEC in the course of the disease is unclear, and there is no consensus regarding pre-operative treatments. In this study we analyzed the effect of neoadjuvant systemic chemotherapy prior to CRS+HIPEC on patients’ outcome.

Methods: Data on consecutive colorectal patients with PC, treated in the Sourasky Medical Center from Jan 2007 to Dec 2016 was collected. Demographic, pathologic and clinical data was registered for all patients. For patients treated with neoadjuvant chemotherapy, the regimen, duration and responses were recorded. Outcome measures were postoperative complications, progression free survival (PFS) and overall survival (OS).

Results: Seventy-two (72) patients were identified, of whom 43 (59.7%) were treated with neoadjuvant chemotherapy and 29 (40.3%) were referred directly to CRS+HIPEC. No significant demographic, pathological or clinical differences between the groups were found. Median PFS was 12 months in the Neo+ group and 17 months in the Neo group (p = 0.015). On multivariate Cox PH analysis, the effect of neoadjuvant chemotherapy on PFS was maintained (HR = 0.34, p = 0.002). Median OS was 41 months in the Neo- and 47 months in the Neo+ with no statistical difference. In the Neo+ group, on univariate analysis, there was no significant effect to chemotherapy regimen, duration of treatment, nor best response. There was no difference in postoperative complication rate between the groups.

Conclusions: In patients candidate for CRS+HIPEC for the treatment of PC from colorectal cancer, the administration of systemic neoadjuvant chemotherapy significantly prolongs PFS with no additional postoperative risks. Prospective randomized trials and larger patient cohorts are needed to confirm these findings and assess the effect on OS.

Legal entity responsible for the study: Tel Aviv University

Funding: None

Disclosure: R. Geva: Advisory board member: Bayer, MSD, Novartis. Honoraria: BMS, Lilly, Medison, Roche, Novartis, Jansen: Travel expenses: Roche, BMS. All other authors have declared no conflicts of interest.

513P Efficacy and tolerability of chronomodulated FOLFIRINOX (chronofLO) as 1st or 2nd line treatment in patients (pts) with metastatic colorectal cancer (mCRC): Final results from an international trial (EORTC 050511)

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Background: FOLFIRINOX is an effective yet toxic protocol against gastrointestinal cancers. We report final updated global results from a randomised international trial aiming to identify the least toxic time of irinotecan (I) combined with Oxaliplatin (O), 5-Fluorouracil (F) and Leucovorin (L).

Methods: 199 MCC pts were randomised to receive chronomodulated I (180 mg/m2 over 6h) on day 1 (d1) with peak delivery at 1:00, 5:00, 9:00, 13:00, 16:00 or 21:00, followed by 4-d fixed-time chronomodulated O (20 mg/m2/d) over 11.5h, with peak delivery at 16:00, alternating with F (700 mg/m2/d) and L (300 mg/m2/d) over 11.5h, with peak delivery at 4:00. ChronofLO was administered every 3rd week using an automatic programmable-in-time pump.

Results: 136 males (68%) and 63 females (32%) were registered at 18 centers. They had a median age of 61 years (range: 30-81, a WHO PS of 0 (73%), 1 (23%) or 2 (4%). ChronofLO was given as 1st (154 pts, 77%) or 2nd line (43 pts, 23%), 14 pts had previously received Ir and 20 pts (O). Pt features were similar in the 6 treatment groups. Median number of cycles was 4 (1-6), and mean relative dose intensities were 88% for F, 86% for O, 89% for C. Overall 3-4 x progression occurred in 136 (199 pts) (67% of pts), nausea (19%), neutropenia (17%), fatigue (13%) and anorexia (11%). 1st line chronofLO achieved an objective response rate (ORR) of 61% [95% Confidence Limits: 53-69], a disease control rate (DCR) of 90% [85-95], a median progression-free survival (PFS) of 8.7 months (mo) [7.6-9.8], and a median overall survival (OS) of 19.3 mo [14.8-24.2].

Conclusions: Chronomodulated triplet showed favourable safety and activity profiles both as frontline or salvage treatment of mCRC, in comparison to previous reports of conventional delivery. The therapeutic index of chronofLO could benefit from the personalisation of drug delivery patterns to match individual differences in internal clock phase.

Clinical trial identification: EORTC 050511

Legal entity responsible for the study: Warwick Medical School

Funding: Warwick Medical School

Disclosure: All authors have declared no conflicts of interest.

514P A multicentre, randomized phase 3 study on the optimization of the combination of bevacizumab with mFOLFOX/XELOX in patients with metastatic colorectal cancer (mCRC)

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Background: Bevacizumab is a humanized anti-vascular endothelial growth factor (VEGF) monoclonal antibody, approved in combination with chemotherapy in the treatment of mCRC. It is proposed that the schedule of administration might be critical
Results: Six patients with FAP were orally administered (3 each in Cohort 1 and 2) CEQ508 in response to CEQ508 in FAP patients. This first-in-human study (START-FAP) aimed to assess the safety, tolerability, and efficacy in response to CEQ508 in patients with familial adenomatous polyposis (FAP).

Significant reduction was observed in overall β-catenin expression in polyps at end-of-treatment (EOT). β-catenin expression levels were measured using qPCR and normalized to housekeeping genes (EUB2, 18S, GUSB). A mixed-model nested-ANOVA was used to evaluate β-catenin knockdown.

Results: Daily oral dosing of 10^4 and 10^5 CFU of CEQ508 for 28 days was well-tolerated. Histology of polyps and normal mucosa at baseline and EOT indicated no changes in tissue morphology or inflammation in cohort 1 patients. A slight inflammation (from score of 0 to 1 at EOT) was noted in normal colon mucosa of cohort 2 patients. Daily oral dosing of 10^5 CFU of CEQ508 for 28 days was well-tolerated with targeted β-catenin knockdown in polyps. β-catenin expression was highest in duodenum and lowest in antrum with no significant treatment effects in normal mucosa. Significant reduction was observed in overall β-catenin expression in polyps at EOT (P < 0.0001). Reduction was observed primarily in the duodenum (39.3%, P < 0.0001) and ileum (28.8%, P = 0.012).

Conclusions: Bacterial delivery of RNAi in FAP patients demonstrated an acceptable safety profile at the two dose levels tested. Without hitting MTD, START-FAP achieved both the primary endpoint of safety and secondary endpoint of β-catenin knockdown. CEQ508 is now being moved into clinical development in combination with Celoxcis/Lisinopril (IT-102) against FAP.

Legal entity responsible for the study: Marina Biotech

Funding: None

Disclosure: V. Trien, L. Hwang: Officers and own stocks for Marina Biotech. All other authors have declared no conflicts of interest.

and that anticipating bevacizumab to chemotherapy, might improve treatment efficacy.

Methods: mCRC patients, ≤ 75 years old, ECOG PS ≤ 1, having received no more than one previous treatment, with at least one measurable lesion according to RECIST, were randomized (1:1) to receive standard administration of bevacizumab (3mg/kg Q4Q) with chemotherapy (mFOLFOX/IRXEL regimen for 12 cycles) vs experimental bevacizumab given 4 days before chemotherapy (same dose), at each cycle. Patients could receive maintenance bevacizumab (7.5 mg/kg Q2Q) until disease progression or unacceptable toxicity in both arms. Primary end point was the objective response rate (ORR). With 80% power and 2-tailed alpha 0.05, an expected 20% increase in response rate, 230 patients were planned. With 163 events, the study also had 80% power to detect a hazard ratio of 0.64 for progression-free survival. Analyses were based on intention to treat.

Results: From May 2012 to Dec 2015, 230 patients were randomly assigned to experimental (n = 115) and standard (n = 115) arm. Median age was 62 (IQR range 53-68); 79% were PS 0, 93% were not pretreated, 54% with a single metastatic site, 52% were PS 0, 94% were not pretreated, 53% had a single metastatic site, 54% were RAS-mutant (47% and 62% in the standard and experimental arm, respectively). ORR was 54% in both arms (p = 0.89). With a median follow-up of 32.4 months, 204 PFS events and 131 deaths were reported. Median PFS was 10.3 and 11.7 months (HR 0.79, 95% CI: 0.60-1.05; multivariate adjusted p = 0.10) and median OS was 23.7 and 29.9 months (HR 0.73, 95% CI: 0.52-1.04; multivariate adjusted p = 0.08), in the standard and experimental arm, respectively. 57% and 51% of the participants received a follow-up treatment in the standard and experimental arm, respectively.

Conclusions: Anticipating bevacizumab to chemotherapy does not improve ORR. A not statistically significant prolongation of PFS and OS was reported in this study. Supported by the Italian Ministry of Health.

Clinical trial identification: EudraCT Number: 2011-004997-27

Legal entity responsible for the study: Istituto Nazionale Tumori, IRCCS, Fondazione G. Pascale

Funding: Italian Ministry of Health

Disclosure: A. Avallone: Travel, accommodation: Roche and Amgen; honoraria for consulting: Roche and Amgen. F. Perrone: Travel: accommodation: Roche, Lilly, Bayer, Daiichi Sankyo; honoraria: Amgen, Novartis, Lilly, Roche, Bayer, Daiichi Sankyo; research funding to institution: Roche and Bayer. M. C. Piccirillo: Travel, accommodation: Roche and Bayer; honoraria for consulting: Bayer. All other authors have declared no conflicts of interest.

Background: TAS-102 is a farnesoid X receptor (FXR) agonist that is orally administered to patients with advanced hepatocellular carcinoma (HCC) in the first-line treatment setting. Recently, the approval of TAS-102 has been obtained in Japan for advanced HCC. To elucidate the activity of this drug in Asian patients in the first-line setting, this study was conducted.

Methods: In this single-arm phase II study, patients with advanced HCC were included. The primary endpoint was ORR and secondary endpoints included PFS, OS, treatment duration and safety. The results of this study were compared with those of a previous report from the Japanese Society of Clinical Oncology (JSCO).

Results: From August 2015 to August 2016, 52 pts were enrolled. Among them, 52 pts received the RP2D as full analysis set. The PFS rate at 16 weeks in pts treated with RP2D. Using a single stage binomial design, this study required 52 pts, with the PFS rate at 16 weeks of 40% deemed promising and 25% unacceptable (alpha = 0.1; beta = 0.2).

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Results: From August 2015 to August 2016, 52 pts were enrolled. Among them, 52 pts received the RP2D as full analysis set. The PFS rate at 16 weeks in pts treated with RP2D. Using a single stage binomial design, this study required 52 pts, with the PFS rate at 16 weeks of 40% deemed promising and 25% unacceptable (alpha = 0.1; beta = 0.2).
Background: Phase 2 data for the combination of ENCO (a selective BRAF inhibitor) + CTX (an anti-EGFR antibody) in pts with BRAFV600E mCRC showed the regimen was well tolerated and improved response rate, progression-free survival, and overall survival compared with historical controls. BEACON CRC (NCT02928224) is a randomized phase 3 study evaluating both the triple combination BINI (a MEK inhibitor) + ENCO + CTX and the doublet combination ENCO + CTX compared with investigators’ choice of irinotecan (IRI). Nineteen pts with BRAFV600E mCRC whose disease has progressed after 1 or 2 prior regimens in the metastatic setting. Here we describe the results of the SIU to determine the safety of the triple combination.

Methods: Nine pts with BRANM mCRC would receive ENCO 300 mg QD and BINI 45 mg BID in 28-day cycles. If >33% of pts had a dose-limiting toxicity (DLT), 16–21 additional pts would be treated at the same dose. If >33% of pts had a DLT, lower doses of BINI and/or ENCO would be assessed.

Results: Thirty pts received the initial dose level; median age was 59 years, 17 pts were female, and 17 had an ECOS PS of 0. DLTs were reported in 5 pts: infusion reaction followed by CTX in pts with BRANM mCRC whose disease has progressed after 1 or 2 prior regimens in the metastatic setting. Here we describe the results of the SIU to determine the safety of the triple combination.

Methods: Nine pts with BRANM mCRC would receive ENCO 300 mg QD and BINI 45 mg BID + CTX 400 mg/m² (then 250 mg/m² QW) in 28-day cycles. If >33% of pts had a dose-limiting toxicity (DLT), 16–21 additional pts would be treated at the same dose. If >33% of pts had a DLT, lower doses of BINI and/or ENCO would be assessed.

Results: Thirty pts received the initial dose level; median age was 59 years, 17 pts were female, and 17 had an ECOS PS of 0. DLTs were reported in 5 pts: infusion reaction followed by CTX in pts with BRANM mCRC whose disease has progressed after 1 or 2 prior regimens in the metastatic setting. Here we describe the results of the SIU to determine the safety of the triple combination.

Aims: To assess the safety, tolerability, and preliminary efficacy of the ENCO + BINI + CTX combination in pts with BRAFV600E mCRC, with or without previous exposure to anti-EGFR agents.

Conclusions: This is the first phase 3 randomized multi-center trial comparing anti-EGFR-agent based regimens with or without bevacizumab. The results of this trial will provide important information on the optimal sequence of anti-EGFR agents and the benefit of bevacizumab in this setting.
Background: Maintenance therapy for mCRC is intended to prolong progression-free survival (PFS) with reduced toxicity, but little information is available concerning the value of epidermal growth factor receptor-targeted antibodies in this setting. Here we present data on outcomes of maintenance therapy from two first-line Pmab trials.

Methods: These retrospective analyses include data from patients with RAS WT (no mutations in KRAS or NRAS exons 2, 3 and 4) mCRC from two randomised trials: PRIME (Pmab vs. FU/FOLOX) and PEAK (FU/FOLOX + either Pmab or bevacaizu).

Maintenance therapy was defined as continuation of the other components of the patient’s study treatment after discontinuation of oxaliplatin. PFS and overall survival (OS) from baseline and from start of maintenance therapy were summarised for patients without progression in each treatment arm.

Results: In PRIME and PEAK, 93 and 61 patients with RAS WT mCRC, respectively, received maintenance therapy (median [IQR] duration: PRIME, 16 [7–37] months; PEAK, 28 [13–41] months). Median PFS and OS overall and from start of maintenance therapy were longer in patients receiving Pmab maintenance vs. controls in both studies (Table).

Conclusions: Even if time to oxaliplatin discontinuation is heterogeneous and patients receiving maintenance treatment are among those with greater treatment benefit, these retrospective data suggest that discontinuation of Pmab-based treatment to 5-fluorouracil/Pmab maintenance is feasible and associated with extended PFS and OS.

Clinical trial identification: PRIME: NCT03364013 PEAK: NCT00819780

Legal entity responsible for the study: Agen

Funding: Agen

Disclosure: F. Rivera Herrero. Advisory boards and/or received research funding from Agen, Bayer, Celgene, Lilly, Merck Serono, MSD, Roche, Servier, and Sanofi. J-B Bachet: Advisory boards and received research funding from Agen, Bayer, Celgene, Merck Serono, Sanofi, and Servier. D.P. Modest: Honoraria and participated in advisory boards for Agen, Bayer, Merck, MSD, Roche, Servier, and SIRTEX, travel support/research funding from Agen, Bayer, Merck, Roche, and Servier. E. de Braud: Advisory boards and consultancy roles for Agen, Eli Lilly, Merck Serono, Roche, and Servier. F. Pietrantoni: Advisory boards and consultancy roles for Agen, Bayer, Eli Lilly, Roche, and Sanofi. R. Koukakis: Employee of Agen Ltd and owns restricted shares in Agen. G. Demonty: Employee of Agen (Europe) GmbH and owns restricted shares in Agen. I.V. Doullard: Steering committee involvement for Agen and Bayer; advisory boards, symposia and consultancy for Agen, Merck Serono, Roche, Sirtex and Takeda; advisory boards for Boehinger Ingelheim and Sanofi; and research funding from Merck Serono.
Multicenter phase II study of biweekly XELIRI plus bevacizumab as a second-line therapy in patients with metastatic colorectal cancer (JSWOG-C3 study)

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Background: Triweekly capcitabine plus irinotecan (XELIRI) is not completely regarded as a valid substitute for fluorouracil, leucovorin, and irinotecan (FOLFIRI) in metastatic colorectal cancer (mCRC) because of the potential for greater toxicity. Therefore, we conducted a phase II study to assess the efficacy and safety of biweekly XELIRI plus bevacizumab (BV) as second-line chemotherapy for mCRC. High dose BV (10 mg/kg) combined biweekly XELIRI as second-line chemotherapy was one of the first trials in the world.

Methods: Patients with mCRC who had received prior chemotherapy including oxaliplatin-based regimens were eligible for this study. Protocol treatment administered capcitabine 1.000 mg/m2 twice daily from the evening of day 1 to the morning of day 6, intravenous irinotecan 90mg/m2 on day 1, and BV 10 mg/kg on day 1 every 2 weeks. The primary endpoint of this study was progression-free survival (PFS) and safety. The secondary endpoint were overall survival (OS), time to treatment failure (TTF), response rate (RR) and disease control rate (DCR).

Results: Between January 2013 and July 2015, 51 patients were enrolled in this study. The patients’ characteristics were as follows: median age, 66 years (range 41-82); male/female, 29/22; The median PFS was 5.7 months (95% confidence interval, 4.2–7.2 months). The median OS was 13.4 months (95% CI, 11.4–16.7 months). The median TTE was 5.2 months (95% CI, 3.9–7.2 months). The response rate was 14%, and the disease control rate was 78%. Grade 3 or higher adverse events were mainly febrile neutropenia in two patients and hypertension in 14 patients (28.6%). One patient had grade 4 intestinal pneumonia but improved by intensive treatment. There were no other severe adverse events or treatment-related deaths.

Conclusions: In mCRC patients, biweekly XELIRI + BV 10 mg/kg is effective and feasible as second-line chemotherapy. Biweekly XELIRI + BV is considered a useful substitute for FOLFIRI + BV in mCRC, and further study of this combination therapy is warranted. Legal entity responsible for the study: Japan Southwest Oncology Group Funding: Japan Southwest Oncology Group Disclosure: All authors have declared no conflicts of interest.
Background: Authors hypothesize that initial anti-VEGF therapy may induce biologic changes that then increase the risk of acquired resistance to subsequent EGFR inhibitors.

Methods: A retrospective cohort study was performed to compare the characteristics and survival of patients who were treated with an anti-EGFR therapy at 2nd line and beyond. We separated two groups defined by the first line therapy, 1. chemotherapy plus bevacizumab (CB) and 2. chemotherapy alone (C). Two survival times were measured for this in this updated analysis: survival from the time of commencing first line chemotherapy and survival from commencement of anti-EGFR therapy. We analysed outcomes separately for the 2L and 3L and beyond groups (3L groups, Long rank (mantel-cox) test analysis was performed to determine whether receiving first line bev was associated with worse overall survival (OS).

Results: 450 mCRC patients who received either CB (n = 249) or C (n = 201), and then an anti-EGFR therapy were studied. Significant differences between CB and C groups for patient characteristics included; decreased median age (61.7 vs. 68.6 years), more females (59.7% vs. 51.0%), more patients with chemotherapy refractory disease (24% v 17%) and increased use of single agent FU (11% v 1.5%). There was no difference in gender (males 65.3% v 66.7%). There was no difference in proportion of patients receiving anti-EGFR second line (2L) CB 39% v C 43%. Where BRAT MT status was assessed 11% had MT (CB 23% v C 0). Median OS for the 2L group, as measured from the commencement of first line therapy, was 24.4 months for CB 18.9 months for C (p = 0.0176). Median OS for the 3L group from the commencement of first line therapy was 32.8 months for CB v 29.9 months for C (p = NS). The survival from commencement of anti-EGFR therapy for CB v C respectively was; 2L 10.5 months v 11.6 months (p=NS), 3L 9.9 months v 8.3 months (p<NS).

Conclusions: Overall survival was significantly improved for CB compared to C when measured from initial treatment. This likely reflects patient selection. Overall survival however from commencement of 2L or 3L anti-EGFR was not altered significantly by prior exposure to bevacizumab in this population based registry.

Legal entity responsible for the study: Adelaide Colorectal Tumor Group

Funding: None

Disclosure: T.J. Price: Advisory board member of Roche, Merck, Amgen. Travel support: Amgen. All other authors have declared no conflicts of interest.

Efficacy of anti-EGFR antibodies combined with chemotherapy for elderly patients with RAS wild-type metastatic colorectal cancer: A systematic review and meta-analysis

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Background: The incidence of Colorectal Cancer (CRC) increases with age, reaching a peak around 70-75 years. The anti-EGFR monoclonal antibodies combined with chemotherapy represent a valid option in patients with RAS wild-type (wt) metastatic CRC (mCRC), allowing a significant improvement in survival. However, few data are available regarding the use of these agents in the elderly population. The aim of the study is to evaluate the efficacy of adding anti-EGFR monoclonal antibodies (Cetuximab or Panitumumab) to chemotherapy in the treatment of RAS wt mCRC older patients.

Methods: A systematic review of the published data using PubMed and EMBASE databases and the congress documents of the main national and international symposia was performed. The random effect model was used to combine the effect estimates, the I2 statistic was used to assess heterogeneity.

Results: Four randomized trials (two regarding Cetuximab and two Panitumumab combined with 5-FU based doublet chemotherapy) have been selected among the 2766 initially identified studies. None of the studies had been specifically designed for the elderly population, so PFS and OS HR values were extracted from pre-specified sub-group analyses. In our study, 665 elderly patients were included: 289 patients received only chemotherapy and 316 patients received chemotherapy in combination with anti-EGFR antibodies. The meta-analysis showed a statistically significant benefit of the combination of chemotherapy and anti-EGFR against chemotherapy alone both in terms of PFS (HR 0.79, 95% CI 0.64-0.98, p = 0.028, Q = 2.54, df = 3, 1-P > 0.05) and OS (HR 0.82, IC 95% 0.68-0.98, p = 0.032, Q = 0.57, df = 3, P > 0.05). The subgroup-analyses confirmed that the Panitumumab studies had a major impact than Cetuximab ones on the final metaanalysis result.

Conclusions: The addition of Cetuximab or Panitumumab to chemotherapy could represent a valid therapeutic option in terms of efficacy, also in elderly patients with mCRC. However, the available data in this subset of patient are limited. Dedicated studies are needed in order to determine the best therapeutic strategy.

Legal entity responsible for the study: Azienda Ospedaliero-Universitaria di Ferrara

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Disclosure: All authors have declared no conflicts of interest.

Efficacy of panitumumab and cetuximab in elderly patients (aged >75) with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (mCRC): Retrospective analysis of data from nationwide drug-reimbursement-access program

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Background: Panitumumab and cetuximab are standards of treatment for chemotherapy-refractory, wild-type KRAS exon 2 mCRC patients. There are limited data on efficacy of these drugs in elderly patients.

Methods: Data were obtained from 2425 patients enrolled into nationwide Panitumumab/Cetuximab Reimbursement-Access Program ongoing in 62 Polish cancer centers. All reported patients were included into study until December 2015. Key inclusion criteria to the program: mCRC, refractory to chemotherapy (5FU, oxaliplatin, irinotecan), aged >18 years, wild-type KRAS exon 2 tumour status, measurable disease, ECOG performance status 0-2. Inclusion and exclusion criteria were the same for panitumumab and cetuximab therapy in all centres. Pre-planned, uniform schedule of efficacy assessment (every 12 weeks) was applied from start of therapy in all centres. Individual patients data concerning efficacy outcome measures were entered prospectively via electronic system into databases of public, national payer - National Health Fund (NFPZ). We performed retrospective analysis using Kaplan-Meier method to assess overall survival (OS) and progression-free survival (PFS). OS and PFS were compared by log-rank test between patients aged <75 and >75.

Results: Out of 2425 patients, 247 were aged >75 years (10%) (165 patients received panitumumab and 82 received cetuximab). In panitumumab group, median OS was comparable in younger and older patients, 9.9 vs 9.6 months, respectively (HR, 1.07; 95% CI: 0.73-1.23; p = 0.6352) (n = 359 v n = 119). In cetuximab group, median OS was also comparable in younger and older patients, 10.2 vs 9.9 months, respectively (HR 0.95; 95% CI: 0.73-1.23; p = 0.6749), as was median PFS, 5.2 vs 5.8 months (HR, 1.08; 95% CI: 0.85-1.38; p = 0.3206) (n = 994 v n = 130). In cetuximab group, median OS was also comparable in younger and older patients, 10.2 vs 9.9 months, respectively (HR 0.95; 95% CI: 0.73-1.23; p = 0.6749), as was median PFS, 5.2 vs 5.8 months (HR, 1.08; 95% CI: 0.85-1.38; p = 0.3206) (n = 994 v n = 130). The subgroup analysis showed no significant differences in efficacy outcomes in younger and older patients in everyday practice.

Legal entity responsible for the study: Military Institute of Medicine, Warsaw National Health Fund, Poland

Funding: None

Disclosure: M. Swierkowski: Consulting role with Pfizer. C. Szczylik: Consulting role with Pfizer, Bayer, Ipsen. All other authors have declared no conflicts of interest.
A difference in CSS (p = 0.0089) and CR (p = 0.014). Corrected for sex, age and renal function, only in the CRT group BSA predicted CSS (OR: 0.248, 95% CI: 0.072-0.857, p = 0.028) and CR (OR: 0.246, 95% CI: 0.083-0.727, p = 0.011). Survival analyses for CAPOX and CRT showed no differences between BSA groups and median survival was comparable to literature.

Conclusions: Flat-dosed cape is safe in CAPOX and MONO. Only in CRT, BSA is predictive for CSS and CR. No survival differences could be identified in subgroups. Therefore, flat-dosed cape is a safe and effective dosing strategy regimens without RT.

Legal entity responsible for the study: Department of Medical Oncology, Erasmus MC Cancer Institute

Disclosure: All authors have declared no conflicts of interest.

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Efﬁcacy of panitumumab and cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (mCRC): Retrospective analysis of data from nationwide drug-reimbursement-access program

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Background: Panitumumab and cetuximab are standards of treatment for chemotherapy-refractory, wild type KRAS exon 2 mCRC patients. There are limited data on efficacy of these drugs in everyday practice on national level.

Methods: Patients enrolled into nationwide Panitumumab/Cetuximab reimbursement-access program ongoing in Polish cancer centres. All reported patients were included to analyses from April 2012 to December 2015. Key inclusion criteria to the program: mCRC, refractory to chemotherapy (5FU, oxaplatin, irinotecan), wild-type KRAS exon 2 tumour status, measurable disease, ECOG performance status 0-2. Inclusion and exclusion criteria were the same for panitumumab and cetuximab therapy in all centres. Pre-planned, uniform schedule of efficacy assessment (every 12 weeks) was applied from start of therapy in all centres. Individual patients data concerning efficacy outcome measures were entered prospectively via electronic system into databases of public, national payer - National Health Fund (NFZ). We performed retrospective analysis using Kaplan-Meier method to assess overall survival (OS) and progression-free survival (PFS). Objective response rate (ORR) was also reported.

As of April 2012, 2425 patients were enrolled into the program in 62 cancer centres (1357 patients received panitumumab and 888 received cetuximab). Median follow-up was 17.9 months for panitumumab and 25.3 months for cetuximab. Median OS was 9.9 months (95% CI 9.4-10.5) with panitumumab and 10.2 months with cetuximab (95% CI 9.5-10.9). There was no OS significant difference between groups (p = 0.09). Median PFS was 5.6 months (95% CI 5.5-5.7) with panitumumab (n = 1124) and 5.2 months (95% CI 4.9-5.4) with cetuximab (n = 619). There was no PFS difference between groups (p = 0.16). ORR was 16% in panitumumab and 13% in cetuximab groups.

Conclusions: Panitumumab and Cetuximab provide similar efficacy outcomes in everyday practice in one health care system. Reimbursement, centralized drug-access programs may serve as a source of data for survival analysis on national level.

Legal entity responsible for the study: Military Institute of Medicine, Warsaw National Health Fund, Poland

Disclosure: None

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Safety phase of phase II study of FOLFOXIRI plus ramucirumab as first-line therapy for patients with metastatic colorectal cancer

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Background: Ramucirumab (Rmab), an anti-VEGFR-2 antibody, inhibits VEG-A, -Fg, -D binding to and blocks circulating VEGF-A. We conducted a phase II study to determine the recommended phase II dose (RP2D) of FOLFOXIRI plus Rmab for metastatic colorectal cancer (mCRC) patients.

Methods: The eligibility criteria included patients with histologically confirmed unresectable colorectal adenocarcinoma, aged 20-75 years, ECOG PS 0-1 (patients > 70 years were eligible if their ECOG PS was 0), wild-type or heterozygous UGT1A1 *28 or -6, no history of prior chemotherapy, and adequate organ function. Three dose levels were planned as follows: oxaplatin and Rmab dose was fixed at 85 mg/m² and 8 mg/kg, respectively. Level 1: S-fluorouracil (S-FU) 3200 mg/m², irinotecan (IRI) 165 mg/m², Level 0 as starting dose: S-FU 2400 mg/m², IRI 150 mg/m², and Level -1: S-FU 2400 mg/m², IRI 120 mg/m². Patients were enrolled with a 3 × 3 design manner to evaluate the dose-limiting toxicity (DLT) in the first cycle.

Results: From September 2016 to February 2017, we enrolled a total of 10 patients (4 patients in the Level 0 and 6 patients in the Level 1). The patients’ characteristics were as follows: median age (range), 64 (44-68); male/female, 6/4; ECOG PS 0/1, 6/4; 6/4 had prior chemotherapy, and adequate organ function. Three dose levels were planned as follows: oxaplatin and Rmab dose was fixed at 85 mg/m² and 8 mg/kg, respectively. Level 1: S-fluorouracil (S-FU) 3200 mg/m², irinotecan (IRI) 165 mg/m², Level 0 as starting dose: S-FU 2400 mg/m², IRI 150 mg/m², and Level -1: S-FU 2400 mg/m², IRI 120 mg/m². Patients were enrolled with a 3 × 3 design manner to evaluate the dose-limiting toxicity (DLT) in the first cycle.

Conclusions: The RP2D for FOLFOXIRI plus Rmab was determined at the Level 1. A randomized phase II study of FOLFOXIRI plus Rmab versus FOLFOXIRI plus Rmab for chemotherapy-naïve mCRC patients (WJOG9161G trial; UMIN000026527) is ongoing. The update results will be presented in the congress.

Clinical trial identification: UMIN000026527

Legal entity responsible for the study: Shizuoka Cancer Center

Funding: Shizuoka Cancer Center

Disclosure: All authors have declared no conflicts of interest.
Prognostic factors and specific populations in the pharmacogenetic randomized phase II trial of FOLFIRI with high-dose (HD) of irinotecan vs standard doses in metastatic colorectal cancer (mCRC) patients (pts) according to UGT1A1 genotype

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Background: Pts with a favourable UGT1A1 genotype (homozygous wild type *1/*1) and heterozygous *1/*28 can be treated with HD of irinotecan without significant adverse events. This randomized phase II trial aimed to evaluate the efficacy and safety of FOLFIRI regimen with HD of irinotecan (HD-FOLFIRI) in mCRC pts. Pts genetically at risk for toxicity (*28/*28) were excluded. Potential prognostic factors and specific population subgroups are presented.

Methods: Chemotherapy-naïve patients with the UGT1A1 *1/*1 or *1/*28 genotypes were randomized to receive HD-FOLFIRI vs FOLFIRI every two weeks. Irinotecan doses for UGT1A1 *1/*1 and *1/*28 pts in the experimental group were 500mg/m² and 260mg/m² respectively. The standard irinotecan dose of 180mg/m² was administered in the control group. Main clinical-pathological characteristics and clinical outcomes of pts included were analysed.

Results: Between Jun-12 and Oct-16 108 pts were included. The ORR was significantly higher in the experimental group (67.5% vs 43.6%, p = 0.001). There were no inter-actions between ORR and clinical characteristics (age, ECOG, tumor location, synchronous disease) and RAS/BRAF status. However, when BRAF mutation was considered, no objective response was observed in the control group compared with 41.5% of pts treated with HD-FOLFIRI (p = 0.005). Metastatic surgical resection was performed in 15 pts (22.5% in HD-FOLFIRI and 15.4% in FOLFIRI) and was associated with ORR (25% vs 5.7%, p = 0.007). Median PFS and OS were 8.6 and 26 months (m) (HD-FOLFIRI) and 8.2 and 29 m (FOLFIRI). ECOC (19.9 vs 7.2 m) and metastatic resection (15.5 vs 7.8 m) were significantly associated with PFS. In terms of OS pts with metastatic surgery (not reach vs 18.4 m) achieved better outcome. Multivariate analysis showed significant association between metastatic resection with both, PFS and OS.

Conclusions: These data confirm the safety of chemotherapy with HD of irinotecan and demonstrate that such strategy improves ORR, which may, in turn, impact favourably on pts survival, especially in those with poor prognosis.

Legal clinical identification: Eudra CT: 2012-000221-42
Legal entity responsible for the study: Instituto de Recerca de l’Hospital de la Santa Creu i Sant Pau
Funding: Spanish Ministry of Health and Social Policy - EC11/336
Disclosure: All authors have declared no conflicts of interest.

A large retrospective multicenter study evaluating prognosis and chemosensitivity of metastatic colorectal cancer with microsatellite instability

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Background: Deficient Mismatch Repair (dMMR) and/or microsatellite instability high colorectal cancers (CRC) represent 12% of all tumours. dMMR non-metastatic CRC are associated with good prognosis but also with resistance to adjuvant 5FU. dMMR metastatic CRC (mCRC) is found in 9% and its influence on prognosis and chemosensitivity is little known.

Methods: This multicenter study included patients with dMMR mCRC treated between 2005 and 2015 in 18 French centers. The Kaplan-Meier method was used to calculate overall survival (OS) and progression-free survival (PFS). Prognostic variables were evaluated in univariate (Log rank test) and multivariate analyses (Cox regression model).

Results: 284 patients with dMMR mCRC were included. Lynch syndrome was found in 43% and BRAF mutation in 32%. Median OS was 25.0 months. Peritoneal carcinomatosis (p < 0.01) and surgery of metastasis (p < 0.01) were associated with OS in univariate analysis but not BRAF mutation and Lynch syndrome. 37% of patients had surgery of metastasis. 79% received first-line chemotherapy (palliative or peri-operative), 46% second-line, 16% third-line. First-line regimens were 5FU-based (n = 20), oxaliplatin-based (n = 106) or irinotecan-based (n = 82) without or with anti-VEGF (n = 71) or anti-EGFR (n = 34). Median PFS on first-line chemotherapy was 5.7 months and in multivariate analysis only surgery of metastasis was associated with PFS (p < 0.01). Median PFS and OS on palliative first-line chemotherapy (n = 149) were 5.9 months and 17.9 months. Median PFS (3.9, 4.4 and 3.0 months, p = 0.20) and OS (17.9, 16.8 and 23.9 months, p = 0.14) were not different according chemotherapy regimen (5FU-based, oxaliplatin-based and irinotecan-based). The addition of bevacizumab or anti-EGFR therapy were associated with a non-significant increased of PFS as compared to chemotherapy alone (4.6, 6.0 and 3.5 months, p = 0.06). Median OS and PFS were 3.5 months and 15.8 months. In third-line, median OS was 6.3 months.

Conclusions: This study suggests that dMMR mCRC are associated with poor prognosis with conventional chemotherapy with or without bevacizumab or anti-EGFR. Only surgery of metastasis was associated with better PFS.

Legal entity responsible for the study: Tougeron David
Funding: None
Disclosure: D. Tougeron: Consulting or advisory role for Amgen, Sanofi, Celgene. Travel or accommodation from Ipsen, Amgen, Sanofi. T. Tenet: Honoraria: Amgen, Merck, Roche, Baxalta, Celgene, Sanofi, Lilly, Sirte. T. Andre: Honoraria: Roche, Bms, Sanofi. All other authors have declared no conflicts of interest.

Exploratory analysis of baseline microsatellite instability (MSI) status in patients with metastatic colorectal cancer (mCRC) treated with regorafenib (REG) or placebo in the phase 3 CORRECT trial

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Background: A high degree of MSI (MSI-H) has been associated with a good prognosis in early-stage CRC. However, emerging evidence suggests that MSI-H patients may have a worse response to chemotherapy in the metastatic setting. Here, we evaluate
survival outcomes by baseline MSI status in patients with mCRC in the CORRECT phase 3 trial.

Methods: CORRECT was an international, multicentre, placebo-controlled trial of 760 patients with treatment-refractory mCRC. Patients were randomized 2:1 to receive oral REG 160 mg or placebo once daily for Weeks 1–3 of each 4-week cycle. Subgroup analysis included patients in the safety population (>1 dose of study drug) who consented to genetic biomarker studies and from whom archival tissue was available. Next-generation sequencing of archival tumor was performed using the FoundationOne gene panel (Foundation Medicine, Cambridge, MA). Overall survival (OS) and progression-free survival (PFS) by MSI status and its potential interaction with treatment were assessed by a Cox proportional hazards model and Kaplan-Meier analysis.

Results: Archival tumor tissue was available for 229 of the 760 randomized patients (Table). Of the 229 patients, 42 (18%) were MSI-H and 187 (82%) were non-MSI-H. 62% were male, 57%–63% were ECOG performance status 0–1, 38% had a KRAS mutation, and 3% had a BRAF mutation. Although there was less clinical benefit in patients in the MSI-H subgroup, no significant association was detected between MSI status and treatment interaction with OS or PFS in the multivariate analysis (P = 0.15).

Table: 534P

<table>
<thead>
<tr>
<th>MSI-H</th>
<th>Non-MSI-H</th>
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</thead>
<tbody>
<tr>
<td>Regorafenib, n (%)</td>
<td>27 (64)</td>
</tr>
<tr>
<td>Placebo, n (%)</td>
<td>15 (36)</td>
</tr>
<tr>
<td>Overall survival, HR (95% CI)</td>
<td>0.97 (0.45, 2.07)</td>
</tr>
<tr>
<td>Progression-free survival, HR (95% CI)</td>
<td>0.78 (0.39, 1.56)</td>
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CI, confidence interval; HR, hazard ratio

Conclusions: This retrospective exploratory analysis of a subgroup of patients with mCRC from CORRECT shows a prevalence of MSI-H at 13–20% and no interaction between MSI status and REG treatment benefit. Due to small sample sizes in the subgroups no firm conclusions can be drawn and further studies are necessary to assess the correlation of MSI status with REG clinical benefit.

Clinical trial identification: NCT01538233

Legal entity responsible for the study: Bayer

Funding: Bayer


536P Docetaxel, cisplatin, and 5-fluorouracil (DCF) chemotherapy in the treatment of metastatic or resectable locally recurrent and squamous cell carcinoma: A phase II study of French interdisciplinary GERCOR and FCD Groups (Epitopes-HPV02 study)


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Background: Anal Squamous Cell Carcinoma (ASCc) is a rare disease, but its incidence is markedly increasing. To date, in advanced ASCc, no standard regimen exists. We have previously published the potential role of DCF regimen. Among 8 advanced ASCC consecutive patients who relapsed after CRT, the DCF regimen induced a complete response in 4 patients, including 3 pathological complete responses. Thus, this study was designed to confirm the interest of DCF regimen in advanced ASCC patients.

Methods: A multicentre phase II trial was conducted among 25 hospitals in France. Main eligibility criteria were histologically proved unresectable locally advanced recurrent or metastatic ASCc, ECOG PS ≤2, and eligible for DCF. Patients received either 6 cycles of standard DCF or 8 cycles of modified DCF depending on age (> 75 years-old) and ECOG-PS (≤ 0.5). The trial was set up based on a Simon’s optimal two-stage design, allowing an early futility interim analysis amid the first 21 patients. The primary endpoint was the observed PFS rate at 12 months from the first DCF cycle. A PFS rate above 25% was expected. With a unilateral alpha error of 5% and a statistical power of 90%, 60 evaluable patients had to be included.

Results: 66 patients were enrolled from September 2014 to January 2017. Median age was 60.05 years (range, 38-78) with female predominance (81.8%). 40 (60.6%) patients had locoregional involvement at enrolment, and the most frequent metastatic sites were liver (60.6%), distal lymph node (48.5%), and lung (36.4%). At interim analysis, 10 (47.6%) patients were progression-free at 12 months from the first DCF cycle. To date, 65 patients are assessable for response rate by investigators. The objective response rates will be 87.9%, including 36.9% of complete responses. Among the first 32 patients with > 12 months of follow-up, 15 (46.9%) patients were progression-free at 12 months.

Conclusions: This first ever conducted prospective trial in front-line advanced DCF demonstrated a high long-lasting response rate of the DCF regimen. DCF regimen should then be considered as a standard of care in this situation.

Clinical trial identification: NCT02402842

Legal entity responsible for the study: University Hospital of Besançon

Funding: Research grant from the University Hospital of Besançon

Disclosure: All authors have declared no conflicts of interest.

537P P2 study of ADXS11-001 Immunotherapy in patients with persistent/ recurrent, surgically unresectable locoregional, or metastatic squamous cell anal cancer

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Background: The number of new anal cancer (SCCA) cases in the US has been rising annually; 20% of patients (pts) will develop metastatic (met) disease, which presents an unmet medical need. A large population-based study showed 88% of SCCA were HPV+ and 73% had HPV-16 (Hoos et al JTC 2009). ADXS11-001 (ADXS) is an irreversibly attenuated Listeria monocytogenes immunotherapy that targets HPV-associated cancers. It is bioengineered to secrete an antigen-adjuvant protein fused to the E7 peptide of HPV-16. It allows the generation of tumor antigen-specific cytotoxic T cells that infiltrate and destroy tumor cells. This is the 1st P2 trial to assess the efficacy/safety of ADXS in met SCCA.

Funding: University of Bradford (Institute of Cancer Therapeutics)

Disclosure: All authors have declared no conflicts of interest.

535P Investigation of MSI status in acquired resistance to 5-fluorouracil treatment in colorectal cancer using a SILAC-based quantitative proteomic analysis method

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Background: Colorectal cancer (CRC) still has a 45% mortality rate, and one of the barriers to therapeutic success is the development of acquired resistance to 5-fluorouracil (5-FU), the most commonly used drug in CRC treatment. Here we establish cell culture models and use state of the art proteomic methods to increase our understanding of how CRC cells develop resistance to 5-FU.

Methods: We develop 5-FU resistant CRC cell lines with different microsatellite stability (MSS) profiles, since MSS is a key genetic alteration in CRC formation, and aim to use these to identify new biomarkers of 5-FU response. 5-FU resistant sublines for 2 cell lines, DLD-1 (microsatellite instability phenotype (MSI)) and HT-29 (MSS), were developed by continuous 5-FU exposure, and resistance fold changes of 150 and 3.5 respectively were achieved. Once 5-FU resistant sublines were developed they were analysed proteomically using a stable isotope labelling with amino acids in cell culture (SILAC) approach and Orbitrap Fusion MALDI Mass Spectrometry analysis, to identify new biomarkers of drug resistance.

Results: A total of 5003 proteins were commonly quantified in the parent cell lines (low and high passage numbers), and in the DLD-1 5-FU and HT 29 5-FU resistant sublines. Six proteins were seen to be significantly up- or down-regulated, and in both 5-FU resistant sublines when compared to the parent cell lines.

Conclusions: This is the first use of a proteomics approach to study protein expression changes in 5-FU resistant CRC cell lines with varying microsatellite stability status, while accounting for changes which occur in the parent lines over the duration of establishing the resistant sublines. We have identified protein changes that correlate both with acquired resistance and the MSI/MSS status, and validated these findings using immunodetection techniques. We are currently extending the CRC study to look at multiple resistance mechanisms for 5-FU with other commonly used CRC therapeutics, oxaliplatin and irinotecan.

Legal entity responsible for the study: Dr. Steve Shyder

Disclosure: All authors have declared no conflicts of interest.

Abstracts

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Methods: This multicenter, open-label, 2-stage design trial (NCT02998813) includes pts ≥ 18 yrs with histologically confirmed, SCCCA and previous > 1 line of therapy for advanced disease. Pts received IV ADXS monotherapy (1x10^9 colony forming units) every 3 weeks for ≤ 2 years or until a discontinue criterion was met. Tumor assessments (RECIST 1.1) were every 9 wks. Interim analysis was planned on enrollment of 31 evaluable pts (≥ 1 post-baseline scan). An objective response rate (ORR) ≥ 30% or a 4-month progression-free survival (PFS) ≥ 20% with tolerable safety would allow proceeding to Stage 2.

Results: Preliminary Stage 1 results are reported with data from 29 of the planned 31 evaluable pts. Median age 60 yrs, range 43-77; 27 F/2 M; median follow-up time 191 days. One pt (3.5%) had a durable partial response lasting ≥ 6 months (after progression on prior anti-EG1-1 therapy) and 7 pts had stable disease (24%). Disease control rate was 28%. The current KM 6-month PFS estimate is 22%. Common (>30%) treatment-related AEs (TRAEs) were grade 1-2 chills/fever/gastro, hypotension and vomiting. Grade 3 TRAEs of cytokine related syndrome (n = 1; SAE), infusion related reactions (n = 2; 1 SAE) and hypotension (n = 2; 1 SAE) were reported.

Conclusions: ADXS monotherapy showed promising activity and met the predefined 6-month PFS rate. Treatment was well-tolerated with mostly grade 1-2 infusion related AEs that resolved successfully with standard care. Further investigation is ongoing in this population.

Clinical trial identification: NCT02998813

Legal entity responsible for the study: Advaxis, Inc

Funding: Advaxis, Inc

Disclosure: C. Eng; Consulting agreement with Advaxis. All other authors have declared no conflicts of interest.

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*BRAF mutant less frequently associated to liver involvement

Background: CTCs, RSAs and BRAF mutations are prognostic factor in mCRC pts. The VisN4Uace; program was designed to explore the impact of FOLFOXIRI + bevacizumab in a high-risk mCRC group according to CTCs > 3 (VisN4uace; -1) and to compare the efficacy of bevacizumab or cetuximab associated to FOLFIRI in a low-risk mCRC group according to CTCs < 3 and WRS wild-type (VisN4uace; -2).

Methods: Blood samples for CTCs enumeration by Cell Search® method (Menarini – Silicon Biosystems, Inc) were collected at baseline, and samples of tumor tissue were used to determine KRAS-NRAS-BRAF-PF3KCA mutations. This preliminary analysis shows the correlation among CTCs, molecular mutations and clinical characteristics by chi-square analysis.

Results: 1208 pts were screened for CTCs and RSAs mutation and 390 of them were eligible for the VisN4Uace; program. In the screening population, CTCs > 3 was found in 40.8%, RSAs, BRAF and PIK3CA mutations were present in 51.4%, 7.5% and 11.3% of pts respectively. No correlation was found among CTCs and RSAs, BRAF and PIK3CA mutations (p<0.01 0.12 respectively). CTCs > 3 was associated with worse ECOG, stage IV, liver and bone metastases, > 2 metastatic sites and CEA levels > 5 mg/ml. CEA mutation correlated with worse ECOG, stage IV, liver, lung and bone metastases, > 2 metastatic sites and CEA level > 5 mg/ml. BRAF mutation correlated with primary right colon location, and metastases in peritoneum, lymph nodes, bone and liver and high tendency for female (p < 0.058) (Table). PIK3CA mutation was only associated with right primary location and age > 65 years.

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Conclusions: CTCs and RAS mutation are significantly associated with other clinical poor prognostic factors. The poor prognosis of BRAF-mutated tumors reported in the literature cannot be explained by its correlation with poor prognostic clinical characteristics.

Clinical trial identification: NCT01640444

Legal entity responsible for the study: Nicola Normanno

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Background: Liquid biopsy can represent an alternative to tissue biopsy for biomarker testing in cancer pts. In addition, liquid biopsy can be used to monitor the response to treatment and the molecular evolution of the disease.

Methods: In the CAPRI GOIM trial, KRAS exon 2 wild type (wt) mCRC pts received first line cetuximab plus FOLFIRI. Tumor samples were assessed by Next Generation Sequencing (NGS) with the Ion AmpliSeq™ Lung and Colon Cancer Panel (ThermoFisher). Plasma samples at baseline (n = 96), at 3 weeks of treatment (n = 54), at 6 weeks (n = 14) and at progression of disease (n = 24) were collected from 96 pts and analyzed for exons 2, 3 and 4 KRAS and NRAS mutations using BEAMing Digital PCR (Syneum Inostics).

Results: Analysis of basal plasma samples from the 96 pts included in this study showed a concordance of 79.2% with the tissue RAS status as defined by NGS. The 11 cases that were RAS mutant (mut) in tissue and wt in plasma had suboptimal plasma volume available for analysis (<3ml), and in 5 cases the only sites of recurrence were lung and/or lymph nodes. Among the 9 cases with wt tissue and RAS mut plasma, all but one had a mutant allelic frequency (MAF) <1%. Plasma samples at 3 weeks were available for 11 pts RAS mut in both tumor and plasma, 6 pts RAS wt in tumor and mut in plasma, and 4 pts were wt in both tumor and plasma. A significant reduction in plasma RAS MAF was observed in all cases at 3 weeks. However, an increase in RAS MAF was observed in all available samples (n = 4) at the progression of the disease. A reduction of MAF after 3 weeks of treatment was also observed in pts who had a RAS positive liquid biopsy with a negative tissue. Among pts with both tissue and plasma basal samples wt, RAS mutations were found in only 1 (3.3%) case after 3 weeks of treatment and in none of the 8 available plasma samples at 6 weeks.

Conclusions: These data suggest that liquid biopsy might better recapitulate the heterogeneity of mCRC and might be useful to monitor the response to therapy. Analysis are ongoing to evaluate the clinical significance of RAS mutations with low MAF.

Clinical trial identification: Eudract number: 2009-18401-81

Legal entity responsible for the study: Nicola Normanno

Funding: Merck Serono, Symex Inostics

Disclosure: Nicola Normanno: Participation to advisory boards and/or research funding from Amgen, AstraZeneca, Merck Serono, MSD, Qiagen, Roche, Symex. E. Maiello, T. Troiani: Participation to advisory boards: Servier and Roche. E. Maiello: Participation to advisory boards: Merck Serono, Roche, Sanofi. F. Ciardiello: Participation to advisory boards and/or research funding from Amgen, Bayer, AstraZeneca, Merck Serono, Roche. All other authors have declared no conflicts of interest.

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540P Analysis of liquid biopsies from metastatic colorectal carcinoma (mCRC) patients (pts) enrolled in the CAPRI GOIM clinical trial

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Background: Liquid biopsy can represent an alternative to tissue biopsy for biomarker testing in cancer pts. In addition, liquid biopsy can be used to monitor the response to treatment and the molecular evolution of the disease.

Methods: In the CAPRI GOIM trial, KRAS exon 2 wild type (wt) mCRC pts received first line cetuximab plus FOLFIRI. Tumor samples were assessed by Next Generation Sequencing (NGS) with the Ion AmpliSeq™ Lung and Colon Cancer Panel (ThermoFisher). Plasma samples at baseline (n = 96), at 3 weeks of treatment (n = 54), at 6 weeks (n = 14) and at progression of disease (n = 24) were collected from 96 pts and analyzed for exons 2, 3 and 4 KRAS and NRAS mutations using BEAMing Digital PCR (Syneum Inostics).

Results: Analysis of basal plasma samples from the 96 pts included in this study showed a concordance of 79.2% with the tissue RAS status as defined by NGS. The 11 cases that were RAS mutant (mut) in tissue and wt in plasma had suboptimal plasma volume available for analysis (<3ml), and in 5 cases the only sites of recurrence were lung and/or lymph nodes. Among the 9 cases with wt tissue and RAS mut plasma, all but one had a mutant allelic frequency (MAF) <1%. Plasma samples at 3 weeks were available for 11 pts RAS mut in both tumor and plasma, 6 pts RAS wt in tumor and mut in plasma, and 4 pts were wt in both tumor and plasma. A significant reduction in plasma RAS MAF was observed in all cases at 3 weeks. However, an increase in RAS MAF was observed in all available samples (n = 4) at the progression of the disease. A reduction of MAF after 3 weeks of treatment was also observed in pts who had a RAS positive liquid biopsy with a negative tissue. Among pts with both tissue and plasma basal samples wt, RAS mutations were found in only 1 (3.3%) case after 3 weeks of treatment and in none of the 8 available plasma samples at 6 weeks.

Conclusions: These data suggest that liquid biopsy might better recapitulate the heterogeneity of mCRC and might be useful to monitor the response to therapy. Analysis are ongoing to evaluate the clinical significance of RAS mutations with low MAF.

Clinical trial identification: Eudract number: 2009-18401-81

Legal entity responsible for the study: Nicola Normanno

Funding: Merck Serono, Symex Inostics

Disclosure: Nicola Normanno: Participation to advisory boards and/or research funding from Amgen, AstraZeneca, Merck Serono, MSD, Qiagen, Roche, Symex. E. Maiello, T. Troiani: Participation to advisory boards: Servier and Roche. E. Maiello: Participation to advisory boards: Merck Serono, Roche, Sanofi. F. Ciardiello: Participation to advisory boards and/or research funding from Amgen, Bayer, AstraZeneca, Merck Serono, Roche. All other authors have declared no conflicts of interest.
and BRAF were most likely to be clonal. EGF, MAP2K1, Ras were generally subclonal. All EGFR ECD mutations emerged in the left colon and all co-existed with RAS mutations plus at least one additional acquired mutation (median 6, range 3-11). RAS/BRAF mutations emerged in 100% and 66% of right and left colon respectively, and co-existed with other RAS acquired mutations in 72% of cases (median, range 1-11). Best response was: PR 8 pts, SD 6 pts and PD 2. In both pts with PD only one acquired mutation was detected at progression (PIK3CA and KRAS respectively), and both mutations were detected in the matching pre-treatment tissue and plasma sample at low MAF. Pts follow-up is ongoing, correlation between mutational profile and response to treatment will be presented.

Conclusions: ctDNA analysis captured intratumor heterogeneity that developed as a result of EGFR inhibition. All EGFR ECD mutations emerged in the left colon and always co-existed with several other mechanisms of acquired resistance, reflecting genomic complexity.

Clinical trial identification: NCT01740703

Legal entity responsible for the study: Japanese Cooperative Group for the Treatment of Digestive Tumors (TTD)

Funding: Public funding from the Ministry of Health, Social Policy and Equality. (TrialRef: EC11-090)

Disclosure: J.M. Viéitez: Consultant or advisory relationship, research funding and honoraria: Amgen. M. Valladares-Ayerbe: Consultant or advisory relationship and honoraria: Roche, Amgen, Merck Serono. E. Aranda Aguilar: For advisory role from Amgen, Bayer, Colgen, Merck, Roche, Sanofi. All other authors have declared no conflicts of interest.

**S43P** Dynamic changes in levels of gene mutations using circulating tumor DNA (ctDNA) and efficacy of 1st-line modified (m)-FOLFOXIRI plus bevacizumab (bev) for metastatic colorectal cancer (mCRC) harboring RAS mutation (mCRC) (JACCRO CC-11)


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Background: FOLFOXIRI plus bev is a standard initial therapy for mCRC but toxic in Japanese patients (pts) due to frequent febrile neutropenia (FN). We performed a phase II trial to assess the safety and activity of 1st-line m-FOLFOXIRI plus bev for mCRC with RAS mut. In addition, pre-planned analysis of a number of genes in ctDNA during therapy that might be determinants of therapeutic efficacy was performed.

Methods: Pts with unresectable/measurable tumors received bev and m-FOLFOXIRI (irinotecan 150 mg/m², oxaliplatin 85 mg/m², levofoilinate (LV) 200 mg/m², and fluorouracil 2400 mg/m², repeated biweekly). After induction therapy for a maximum of 12 cycles, maintenance therapy with fluorouracil/LV plus bev was administered. The primary endpoint was objective response rate (ORR). Progression-free survival (PFS), overall survival, early tumor shrinkage (ETS), depth of response (DpR), and safety were secondary endpoints. Plasma samples for extraction of ctDNA were collected at 3 points (pre-, 8w, and progression) and analyzed for specific KRAS, NRAS, BRAF, and PIK3CA variants with real-time PCR assays.

Results: Survival of 64 participants evaluable for efficacy had the following characteristics: median age 63, 55% male, 92% PS0, and 27% right-sided tumors. Median follow-up time was 7.9 months. ORR and disease control rate were 74.2% and 96.8%, respectively. ETS was 74%, and median DpR was 48%. Median PFS was not reached.

Common grade 3 or 4 adverse events were neutropenia (49%), hypertension (22%), diarrhea (13%), and FN (4.8%). No treatment-related deaths occurred. Analysis of ctDNA from pre-treatment plasma confirmed mts in 72% (38/53) of pts. Absence of mt at 8w correlated with ORR regardless of KRAS status at pre-treatment (na mt; 80% (32/40), any mt; 45% (5/11), P = 0.05, t-test); moreover, pts with PIK3CA mt at pre-treatment had a poor response (43%, 3/7).

Conclusions: m-FOLFOXIRI plus bev is active and feasible for Japanese mCRC pts with RAS mt. KRAS, NRAS, and PIK3CA mt in ctDNA were associated with response to the triplet plus bev and might potentially be used to predict outcomes.

Clinical trial identification: UMIN000015152, Oct/1/2014

Legal entity responsible for the study: Japan Clinical Cancer Research Organization: JACCRO

Funding: Japanese Clinical Cancer Research Organization: JACCRO

Disclosure: Y. Sunakawa: Honoraria from Taiho Pharmaceutical, Chugai Pharma, Yakult Honsha, Takeda, and Merck Serono. H. Satake: Honoraria from Bayer, Chugai Pharma, Eli Lilly Japan, Merck Serono, Takeda, Taiho Pharmaceutical, and Yakult Honsha. M. Nakamura: Honoraria from Merck Serono, Taiho Pharmaceutical, Yakult Honsha, M. Kotaka: Honoraria from Chugai Pharma, Yakult Honsha, Daiichi Sankyo, M. Takeuchi: Honoraria from Mitsubishi Tanabe Pharma, consulting or advisory role from Hisamitsu Pharmaceutical, Kowa, Taiho Pharmaceutical, Shionogi Pharma, Abbvie, AstraZeneca Japan and EA Pharma, travel grants from AstGen MG, Inc. H-J. Lenz: Consulting or advisory role for Merck Serono, Roche, Bayer, and Pfizer, travel expenses from Merck Serono, Bayer, and Roche, honoraria from Merck Serono, Roche, Bayer and Boehringer-Ingelheim. W. Ichikawa: Consulting role from Daiichi Sankyo, Zeria Pharmaceutical, Otsu Pharmaceutica, honoraria from Merck Serono, Taiho Pharmaceutical, Chugai Pharma and Takeda, research funding from Takeda, Taiho, Eisai, Merck Serono, Otsu, Chugai and Shionogi. All other authors have declared no conflicts of interest.

**S44P** The frequency of RAS mutation in circulating tumor DNA predicts worse survival in patients with mCRC

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Background: RAS mutations predict a worse prognosis in metastatic colorectal cancer (mCRC). However, there are few findings regarding the prognostic value of RAS mutations in circulating tumor DNA (ctDNA). We aimed to compare the concordance of genomic alterations between ctDNA and tissue biopsies and assess the prognostic value of RAS mutations in ctDNA.

Methods: Gene mutation status in plasma and tissue were evaluated in mCRC patients by next-generation sequencing (NGS). Kaplan-Meier curve and Cox regression model were used to compare the progressive free survival (PFS) between different level of RAS mutations frequency.

Results: Of NGS testing from tumor tissue and ctDNA from 110 sequential mCRC patients were compared. Analysis of 6 gene in baseline tissue and plasma samples showed a 67.3% overall agreement. Concordance between the two platforms for KRAS, NRAS, BRAF, PIK3CA, SNAIA and FBXW7 mutations were 80.9%, 98.2%, 92.9%, 91.8%, 69.1%, 93.6% and 96.4%, respectively. RAS mutation rate in tissue and ctDNA were 41.8% and 29.1%. Fifty-nine patients were detected RAS mutation in tumor tissue, only thirty-six patients with plasma RAS mutation. One patient was detected dCtDNA RAS mutation without mutation in tissue. Across plasma RAS gene, sensitivity and specificity were 61.0% and 99.3%, respectively. With a 48.2% cut-off rate, we divided 59 tissue RAS mutation patients into two different dCtDNA RAS mutation groups (high frequency and low frequency group). Median PFS in high frequency group was 1.9 months and in low frequency group was 4.8 months (P = 0.002). In multivariate analysis considering other clinical factors (i.e. synchronous or metachronous metastases and CEA level, high ctDNA KRAS mutation frequency was independent adverse prognostic factor (HR 4.09, 95% CI 1.61-10.40, P = 0.003) for PFS in tissue KRAS mutation patients.

Conclusions: Plasma and tissue NGS testing have a high concordance in genomic alterations. Higher rate of baseline KRAS mutation frequency predicts worse prognosis in mCRC. Both plasma and tissue NGS may be necessary to describe the complex biology of mCRC. Circulating tumor DNA testing could be a viable alternative for genotyping of mCRC and recommended for routine clinical practice.

Legal entity responsible for the study: None

Funding: None

Disclosure: All authors have declared no conflicts of interest.
However, it was predictive of Pan benefit: in gain was significantly associated with high EREG and AREG RNA expression (both Results:
196 (71.3%) pts were classified as EGFR gain and 79 (28.7%) as normal. EGFR array, analysed using Biodiscovery Nexus software and defined as normal (2 copies) or
utility.

Legal entity responsible for the study:

Disclosure:

Funding:

Affymetrix

Long-term follow-up analysis of pts enrolled in the CAPRI-GOIM trial showed a median OS of approximately 36 m in KRAS, NRAS, BRAF and PIK3CA wt pts. A better prognostic outcome in terms of OS and PFS was observed in left-sided as compared to right-sided tumors.

Clinical trial identification: EudraCT number 2009-01441-81

Legal entity responsible for the study: Gruppo Oncologico dell’Italia Meridionale (GOIM)

Funding: Cetuximab was provided by Merck Serono. Other funding: AIRC.

Disclosure: E. Martinelli: Advisory Board: Merck Serono, Roche, Amgen, F. Cardiello: Advisory Board: Merck Serono, Roche, Amgen, Pfizer, Bayer, Lilly. All other authors have declared no conflicts of interest.

Background:

In metastatic colorectal cancer (mCRC) recent studies have shown the importance to accurately quantify low-abundance mutations of RAS pathway because response to anti-EGFR therapy may depend on certain mutation thresholds. We designed a clinical trial to compare clinical outcomes of patients selected with different analytical sensitivity thresholds for RAS/BRAF mutated alleles using a highly sensitive and quantitative technique of digital PCR (dPCR).

Methods: Hotspots including RAS (KRAS and NRAS exons 2/3/4) and BRAF (exon 15) were prospectively analysed in tumour FFPE samples from 61 patients with mCRC included in the ULTRA trial. Patients had received one or two previous chemotherapy lines and were deemed resistant to irinotecan. Response rate (RR), progression-free survival (PFS) and overall survival (OS) were correlated with the mutational status based on three different cut-off points (0.1%, 1% and 5%).

Results: The overall RR was 51.7% and comparative analysis of clinical outcomes trans- formed into a differential progression free survival (PFS), response rate (RR) and progression disease (PD) in the different cohorts defined by the 3 selected analytical sensitivity cut-off points (Table). PFS prediction was higher when we considered a threshold of 5% in RAS/BRAF scenario (HR mut vs wt = 3.85; CI95% [1.16-12.82], p = 0.018).

Conclusions: Optimal sensitivity RAS/BRAF mutational analysis cut-off for clinical outcome prediction lies between 1 and 5% (closer to 5%). Increasing analytical sensi- tivity worsens patients’ selection. Further sensitivity threshold comparative analysis will define an optimal cut-off.
BRAFV600E and KRAS mutations are shown to have inferior relapse-free survival, as previously shown to be associated with BRAF and KRAS mutations, respectively. We used CMS classification in the analysis and supplemented with gene expression data for 514 patients. To increase the number of samples with MSI status, we determined mutation analysis for hotspots in KRAS and BRAF according to microsatellite instability (MSI) status and KRAS/BRAF mutation. A total of 1197 primary tumor samples from a consecutive series of patients treated surgically for stage I–IV CRC at Oslo University Hospital, Norway, were collected for all patients. Mutation analyses were performed for hotspots in KRAS and BRAF genes. Concordant mutations were shown poor outcomes in several clinical trials, but its biological role has not been fully elucidated. Classification of CRCs according to gene expression profiling and methylome analysis remains controversial with regards to their ability to stratify patients for precision therapy.

**Methods:** We performed miRNA microarray analysis and used pathway analyses by Gene Set Enrichment Analysis (GSEA) in the following three subsets: eight BRAF-mutant CRC tissues without MSI, six BRAF-mutant CRCs with MSI and five BRAF-wild type CRCs with MSI. Following identification of candidate biomarkers that affect poor outcomes and associate with BRAF V600E mutation, we examined epigenetic variations of these candidate biomarkers in a cohort of 1008 CRC patients who underwent surgical resection of their primary tumor and/or metastatic lesions from 1994 to 2015 at the Okayama University Hospital.

**Results:** Prominent signatures enriched in CRCs with BRAF V600E mutation were EMT-related processes (EMT and myogenesis), Wnt signaling and intestinal differentiation-related genes. Among the differentially expressed genes, Secreted frizzled-related proteins (SFRPs) were significantly upregulated in BRAF V600E mutant CRCs compared with wild type CRCs with MSI, and six BRAF-mutant CRCs with MSI, showing poor outcomes in several clinical trials, but its biological role has not been fully elucidated. Classification of CRCs according to gene expression profiling and methylome analysis remains controversial with regards to their ability to stratify patients for precision therapy.

**Table: 547P**

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<td>37.5/52.8</td>
<td>33.3/51.7</td>
</tr>
<tr>
<td>SD % (mut/wt)</td>
<td>46.2/33.3</td>
<td>50.0/94.0</td>
<td>33.3/36.2</td>
</tr>
<tr>
<td>PO % (mut/wt)</td>
<td>7.7/12.5</td>
<td>12.5/11.3</td>
<td>33.3/10.3</td>
</tr>
</tbody>
</table>

**Background:** In the present study we report the distribution and prognostic impact of KRAS and BRAF mutations according to microsatellite instability (MSI) status and consensus molecular subtypes (CMS) in colorectal cancer (CRC).

**Methods:** A total of 1197 primary tumor samples from a consecutive series of patients treated surgically for stage I–IV CRC at Oslo University Hospital, Norway, were collected for all patients. Mutation analyses were performed for hotspots in KRAS (exon 2: codons 12 and 13, exon 3: codon 61) and BRAF (exon 15: codon 600) and MSI-status was determined. A subset of samples were analyzed for gene expression using exon-level microarrays and classified according to the CMS groups of CRC, with confident classification obtained in 317 samples. To increase the number of samples with CMS classification the analysis was supplemented with gene expression data for 314 patients in the publically available dataset GSE39082, including also MSI status, BRAF and KRAS mutation status, as well as clinical data. Gene expression signatures previously shown to be associated with BRAF and KRAS mutations, respectively, were used to evaluate differential impact of mutations on gene expression among CMS groups.

**Results:** BRAFV600E and KRAS mutations are shown to have inferior relapse-free survival in MSI tumors exclusively (BRAF mut vs KRAS/BRAF wt: Hazard ratio (HR) 2.35 (1.71–3.22); p = 0.001 and KRAS mut vs KRAS/BRAF wt: HR 1.23 (1.01–1.49); p = 0.044). Stratifying the survival analysis according to CMS groups reveals the negative prognostic impact of BRAFV600E mutations to be specific to MSS tumors in CMS1 (BRAF mut vs wt: HR 4.96 (1.74–14.12); p = 0.003), while KRAS mutations are associated with poor prognosis distinctively in MSS tumors in CMS2 (KRAS mut vs wt: HR 1.60 (1.11–2.30); p = 0.011). Further, the effects of BRAF and KRAS mutations on gene expression signatures are shown to vary according to MSI-status and CMS subtype, substantiating the subtype-specific associations.

**Conclusions:** BRAFV600E mutations have poor prognostic value specific to MSS tumors in CMS1, while KRAS mutations are associated with adverse outcome in MSS tumors in CMS2.

**Legal entity responsible for the study:** Oslo University Hospital

**Funding:** None

**Disclosure:** All authors have declared no conflicts of interest.
BRAF mutation is associated with poor survival in colorectal cancer. We aimed to generate genomic signature associated with BRAF mutation that possibly predict prognosis in colorectal cancer. **Methods:** A gene expression signature reflecting BRAF mutation was generated in TCGA cohorts (n = 207). The colorectal cancer patients were stratified into two groups according to this signature: BRAF mutation type colorectal cancer or BRAF wild type colorectal cancer. Prognostic significance of BRAF mutation-associated signature was tested in two other cohorts (GSE 17538, GSE 14335). **Results:** The BRAF mutation signature was associated with poor prognosis in two independent cohorts (total n = 522). BRAF mutation signature was associated with poor disease-free survival (median: not reached, P = 0.003) in GSE14335, and associated with poor overall survival (P = 0.019, median: 37.3 months vs. not reached). In a multivariate analysis, BRAF mutation signature was independent poor prognostic factor for disease-free survival (hazard ratio 2.1, 95% CI 1.43-2.62; P = 0.001). Gene network analyses suggested epithelial-mesenchymal transition is the possible explanation for poor prognosis of BRAF mutation colorectal cancer. **Conclusions:** BRAF mutation signature is highly associated with poor prognosis in colorectal cancer and the molecules associated with epithelial-mesenchymal transition can be potential treatment targets in BRAF mutation colorectal cancer. Legal entity responsible for the study: Chonnam National University Hwasun Hospital, Republic of Korea

Funding: None

Disclosure: All authors have declared no conflicts of interest.

**Abstract:**

**Background:** BRAF mutation is associated with poor survival in colorectal cancer. We aimed to generate genomic signature associated with BRAF mutation that possibly predict prognosis in colorectal cancer. **Methods:** A gene expression signature reflecting BRAF mutation was generated in TCGA cohorts (n = 207). The colorectal cancer patients were stratified into two groups according to this signature: BRAF mutation type colorectal cancer or BRAF wild type colorectal cancer. Prognostic significance of BRAF mutation-associated signature was tested in two other cohorts (GSE 17538, GSE 14335). **Results:** The BRAF mutation signature was associated with poor prognosis in two independent cohorts (total n = 522). BRAF mutation signature was associated with poor disease-free survival (median: not reached, P = 0.003) in GSE14335, and associated with poor overall survival (P = 0.019, median: 37.3 months vs. not reached). In a multivariate analysis, BRAF mutation signature was independent poor prognostic factor for disease-free survival (hazard ratio 2.1, 95% CI 1.43-2.62; P = 0.001). Gene network analyses suggested epithelial-mesenchymal transition is the possible explanation for poor prognosis of BRAF mutation colorectal cancer. **Conclusions:** BRAF mutation signature is highly associated with poor prognosis in colorectal cancer and the molecules associated with epithelial-mesenchymal transition can be potential treatment targets in BRAF mutation colorectal cancer. Legal entity responsible for the study: Chonnam National University Hwasun Hospital, Republic of Korea

Funding: None

Disclosure: All authors have declared no conflicts of interest.
dehydrogenase: 340 U/L (1QR: 195) received a mean (SD) of 8.3 (5.5) P cycles and 7.7 (4.8) C cycles. 81% and 62% of pts received ≥80% of relative dose intensity of P and C, respectively. Confirmed ORR was 38%, with 69% of pts achieving at least stable disease. Median (95%CI) DoR was 8.7 (6.2-12.7) months, and median TTR was 2.2 (1.8-3.2) months. Median (95%CI) TTP was 9.9 (3.5-12.0) months, with a median TTF of 5.4 (3.1-9.1) months. The median (95%CI) PFS was 9.6 (3.5-11.5) months, and the median OS was 23.7 (12.0-27.5) months. 14 (54%) pts reported grade 3/4 adverse events (Table). There were no cases of neutropenia, thrombopenia or toxic deaths.

**Table: S53P Incidence of adverse events**

<table>
<thead>
<tr>
<th>Grade 1-2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>3 (12%)</td>
<td></td>
</tr>
<tr>
<td>Paronychia</td>
<td>2 (8%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Rash</td>
<td>3 (12%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Mucositis</td>
<td>5 (19%)</td>
<td></td>
</tr>
<tr>
<td>Skin toxicity</td>
<td>10 (39%)</td>
<td>4 (15%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (15%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Hand-Foot Syndrome</td>
<td>1 (4%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>4 (15%)</td>
<td>1 (4%)</td>
</tr>
</tbody>
</table>

**Conclusions:** These preliminary results suggest that panitumab plus capecitabine is a safe and effective regimen in elderly patients with WT KRAS mCRC.

Clinical trial identification: The number of trial protocol: 2012-00751-13 The realize date (when it was obtained): 2012-06-18

Legal entity responsible for the study: Agen

Funding: None

Disclosure: All authors have declared no conflicts of interest.

**SS4P**

Prevalence of KRAS/NRAS/BRAF mutations detected by massive parallel sequencing and differential outcomes in MCRC patients (pts) treated with first line FIr-B/FOX adding bevacizumab (BEV) to BEV chemotherapy


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**Background:** KRAS/NRAS/BRAF mutations guide tailoring of first and subsequent regimens. BRAF15 and NRAS2-4 mutations guide tailoring of first and subsequent regimens. However, despite the availability of validated biomarkers, there is a need for further studies on the role of additional biomarkers.

**Methods:** Tumor samples of 67 MCRC pts treated with FIr-B/FOX (77% overall) were analyzed through a 50 genes panel (PGM/Colon Lung Cancer) by ION Torrent. KRAS exon 2-4, NRAS exon 2, BRAF exon 15 were evaluated. The candidates were selected for a minimum of 500 sequence coverage. Clinical outcomes (PFS and OS) were evaluated and compared by log-rank.

**Results:** KRASmut were 42 (62.7%), of which 21 (50%) were conserved (without other somatic alterations in the same codon); 21 (50%) were not conserved (with other somatic alterations in the same codon). NRAS mut were 13 (19.4%) and BRAF mut were 5 (7.9%). KRASNRASmut, and BRAF mut MCRC patients were 49 (77.8%), wt 14 (22.2%); single gene mut 40 (63.5%), KRASmut (54%), and NRASmut (9.5%); ≥1 mut genes 9 (14.3%), double mut and triple mut 4, specifically double BRAF15, NRAS2-4, BRAF15, double NRAS2-4. BRAF15 mut were all atypical and consommented with KRAS and/or NRAS mutations. Prevalence of KRASmut, NRASmut, and BRAFmut were 19%, 53.8%, and 100% of each mut gene. At median follow-up 21 months (m), PPS and OS overall, and of KRASmut genotype were consistent with previously reported; in ≥.33 G > A, BRAF15 mut trendly worse PFS m and OS 14 m. Differential clinical outcome of MCRC patients wt and mut were not significantly different: KRASmut, PFS 13 and 12 m, OS 27m and NRASmut, PFS 16 and 12 m, OS 28 and 22m; BRAF15 mut OS 14 and 8 m, OS 28 and 11 m; KRASNRASmut, BRAF15 mut OS 18 and 12m, OS 28 and 22m.

**Conclusions:** Clinical outcome of MCRC patients treated with FIr-B/FOX is not significantly affected by KRAS, NRAS, and BRAF15 mut; genotype; efficacy may be increased in triple wt patients; the prevalent c.33 G > A KRAS and BRAF mut may work worse prognosis.

Legal entity responsible for the study: Enrico Ricevuto

Funding: None

Disclosure: All authors have declared no conflicts of interest.

**Table: S55P Correlation of VEGF-D with Efficacy Outcomes: based on cut point from exploratory subset. Results below from combined exploratory + confirmatory groups**

<table>
<thead>
<tr>
<th>Prespecified cut point</th>
<th>≥115 pg/mL</th>
<th>&lt;115 pg/mL</th>
<th>PFS</th>
<th>≥115 pg/mL</th>
<th>&lt;115 pg/mL</th>
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<tbody>
<tr>
<td><strong>Patients</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Median (months) (95% CI)</td>
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<td></td>
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<td></td>
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<tr>
<td>19.9 (15.6, 24.2)</td>
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<tr>
<td>12 (10.1, 14.0)</td>
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<td>13.2 (12.2, 14.0)</td>
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<tr>
<td>6.0 (5.6, 7.0)</td>
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<tr>
<td>4.0 (4.2, 5.0)</td>
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<tr>
<td>5.4 (5.3, 6.9)</td>
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<tr>
<td>1.16 (0.93, 1.45)</td>
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<td>0.1930</td>
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<tr>
<td><strong>HR (95% CI)</strong></td>
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<td>0.0022</td>
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<td>0.0344</td>
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</table>

**Background:** The RAISE trial (NCT01183780) demonstrated that RAM plus FOLFIRI (leucovorin, fluorouracil, and irinotecan) significantly improved overall survival (OS) and progression-free survival (PFS) compared with placebo plus FOLFIRI (PBO) as second-line mCRC treatment. Despite multiple approved anticancer treatments targeting angiogenesis, there are currently no predictive markers to guide patient selection. The extensive RAISE biomarker program assessed the association of multiple candidate biomarkers with RAM efficacy outcomes.

**Methods:** Plasma and tumor tissue collection was mandatory in the RAISE trial. Analyses were performed using exploratory assays to assess the correlations of the baseline marker levels (vascular endothelial growth factor [VEGF] C and D, soluble vascular endothelial growth factor receptor [VEGFR] 1, 2, and 3, and VEGFR2 immunohistochemistry in tumor tissue) with clinical outcomes. Cox regression analyses adjusted for stratification factors were performed for each marker.

**Results:** Biomarker results were available from ≥80% of patients. Among the candidate biomarkers analyzed, only VEGF-D levels had a consistent and statistically significant association with OS and PFS, suggesting a predictive relationship. Higher levels were associated with improved RAM efficacy (Table). This relationship was consistent across the full range of VEGF-D levels.

**Conclusions:** These analyses from RAISE identified VEGF-D as a potential predictive marker for RAM efficacy in mCRC. Further investigation of this relationship is being pursued.

Clinical trial identification: NCT01183780

**Table: S55P Correlation of VEGF-D with Efficacy Outcomes: based on cut point from exploratory subset. Results below from combined exploratory + confirmatory groups**

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<table>
<thead>
<tr>
<th>Prespecified cut point</th>
<th>≥115 pg/mL</th>
<th>OS</th>
<th>&lt;115 pg/mL</th>
<th>PFS</th>
<th>≥115 pg/mL</th>
<th>&lt;115 pg/mL</th>
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<td><strong>Patients</strong></td>
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<tr>
<td>Median (months) (95% CI)</td>
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<td>6.0 (5.6, 7.0)</td>
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<td>4.0 (4.2, 5.0)</td>
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<td>1.16 (0.93, 1.45)</td>
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<td><strong>HR (95% CI)</strong></td>
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<td>0.73 (0.60, 0.89)</td>
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<td>0.32 (0.22, 0.46)</td>
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<td>0.62 (0.52, 0.74)</td>
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<tr>
<td>0.1930</td>
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</table>
A novel CpG panel is independently associated with colorectal cancer survival

M. Li1, Y. Zhang1, L. Jansen1, W. W. van der Graaf1, T. Aparicio1, T. T. V. de Vries1, S. F. van der Ploeg2, A. J. N. van der Pluijm1, E. J. A. van Drunen-Laschat1, J. A. G. van Solinge2, J. A. van der Leest3, M. S. van der Ende4, M. van de Velde1, J. A. M. van ’t Veer1, E. J. Franssen1, R. J. M. van de Wijer1, E. van Beers-Schreuder1

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Division of Molecular Epidemiology, German Cancer Research Center, Heidelberg, Germany.

Institute of Pathology, University Medical Center Mainz, Mainz, Germany.

Core Facility Genomics & Proteomics, German Cancer Research Center, Heidelberg, Germany.

Department of General Practice, Route of Pathology, University of Heidelberg, Heidelberg, Germany.

Department of Applied Tumor Biology, Institute of Pathology, Heidelberg University Hospital, Heidelberg, Germany.

Department of Visceral and Transplantation Surgery, University of Heidelberg, Heidelberg, Germany.

Charité University Medicine, Institute of Pathology, Berlin, Germany.

Division of Cancer Epidemiology, Unit of Genetic Epidemiology, German Cancer Research Center, Heidelberg, Germany.

Background: Results of previous studies on the association of the CpG island methylator phenotype (CIMP) with colorectal cancer (CRC) prognosis differed. The variety of markers selected to define CIMP was widely blamed for the inconsistency. The current study was therefore aimed to comprehensively investigate the association of DNA methylation at CIMP-related genes with CRC survival.

Methods: Patients with CRC diagnosed between 2003 and 2007 were followed up for a median of 5.2 years and divided into a screening cohort (n = 568) and a validation cohort (n = 308). DNA methylation was measured in tumor tissue using the Illumina Infinium HumanMethylation450 BeadChip. Cox proportional hazard regression models were used to estimate adjusted hazard ratios (HR) and 95% confidence intervals (CI) of survival after CRC, including adjustment for tumor stage, microsatellite instability, BRAF mutation status and other important factors.

Results: Of 48 genes used to define CIMP in the previous studies, 43 were also covered by the methylation array. In the screening cohort, ten CpG sites were identified to be independently associated with colorectal cancer survival, seven of these ten CpG sites were also associated with CRC survival in the validation cohort.

Conclusions: A CpG panel consisting of seven CpG sites was found to be strongly associated with CRC survival, independent from important clinical factors and mutations associated with CIMP.

Legal entity responsible for the study: Division of Clinical Epidemiology and Aging Research, German Cancer Research Center

Funding: German Research Council, the German Federal Ministry of Education and Research.

Disclosure: All authors have declared no conflicts of interest.
SS5P High PD-L1 expression and high CD8+ T-cell infiltration identifies a new subpopulation of colorectal cancer with high risk of relapse and poor outcome

M. Faliki1, C. Ouyang1, C. Wang1, T.Y. Tu1, M. Cho1, M. Sy1, J. Longmate1, P.P. Lee1
1Medical Oncology, City of Hope, Duarte, CA, USA, 2Office of Chief Informatics, City of Hope, Duarte, CA, USA, 3Immunology-Oncology BRI, City of Hope, Duarte, CA, USA, 4Information Sciences - BRI, City of Hope, Duarte, CA, USA

Background: CD8+ T-cell primary tumor infiltration is associated with improved colorectal cancer (CRC) outcome. However, the interaction between CD8+ T-cell infiltration and intra-tumor PD-L1 expression has not been previously characterized. This study aims to explore the impact of PD-L1 expression and degree of CD8+ T-cell infiltration on the outcome of patients with stage II and III CRC.

Methods: CD8, PD-L1, PD-L2, cytokinin 20, and CD68 expression were quantified via multi-spectral immunohistochemistry of primary CRC tumors from 35 patients with recurrent disease (cases) and 36 patients without recurrence (controls). The TCGA (The Cancer Genome Atlas) and the NCBI-GEO (Gene Expression Omnibus) datasets of 385 and 828 stage II-III cases, respectively, were used to validate the prognostic value of the discovery set biomarkers, both for relapse free survival (RFS) and overall survival (OS).

Results: In the 71 patient discovery case-control set, densities of CD8+ and PD-L1+ cells in tumor microenvironment classified patients into three distinct populations. High CD8+ cell infiltration (above median) and high PD-L1 expression (>90 percentile) was associated with best outcome among all patients with CD8+PD-L1hi experienced disease relapse, despite being enriched in mismatch repair deficiency (4 patients). Low CD8+ cell infiltration was associated with a high relapse rate irrespective of PD-L1 status: 80% of patients with CD8+ relapsed. CD8hi in the absence of high PD-L1 expression (CD8hi/PD-L1−) had the lowest risk of relapse: 31% of patients relapsed. The validation data sets confirmed that the CD8hi/PD-L1+ and the CD8+ groups carried an inferior RFS (NCBI-GEO data set: HR = 1.655, p = 0.002) and OS (TCGA data set: HR = 3.556, p = 0.0009) in comparison to the CD8hi/PD-L1− group.

Conclusions: CD8hi/PD-L1+ defines 10% of patients with stage II/III CRC and confers a higher risk of relapse, despite enrichment with MMR deficiency. This subgroup of patients may be suitable for the investigation of PD-1 checkpoint inhibitors.

Legal entity responsible for the study: City of Hope

Disclosure: All authors have declared no conflicts of interest.

SS59P Clinical impact of molecular positive lymph node status in colorectal cancer

N. Matsuda1, N. Tomita1, M. Inomata2, K. Murata1, S. Hayashi1, Y. Miyake3, S. Igarashi1, M. Hatada1, T. Kato1, S. Nozaki1, F. Furuhata5, H. Ozawa1, T. Takemasa1, M. Yasui1, H. Taleyeb1
1Surgery, Osaka International Cancer Institute, Osaka, Japan, 2Surgery, Hyogo College of Medicine, Nishinomiya, Japan, 3Gastroenterological and Pediatric Surgery, Faculty of Medicine, Osaka University, Osaka, Japan, 4Pathology, National Hospital Organization Osaka National Hospital, Osaka, Japan, 5Surgery, Osaka International Medical College, Osaka, Japan

Background: Accurate evaluation of lymph node (LN) status is important for prediction of prognosis and decision of postoperative adjuvant therapy in cancer patients. Histopathological diagnosis, usually used for this evaluation, has shortcoming of lower sensitivity due to observing only small portion of whole lymph node. To overcome it we examined whole LN, which could be cut into half hematoxylin-eosin staining. In addition, half of the LN, which could be cut into half, was used for one-slice hematoxylin-eosin staining.

Methods: Patients with cN0 and cN1 CRC in 11 Japanese representative medical institutes were enrolled. All LNs were examined histopathologically by using one-slice hematoxylin-eosin staining. In addition, half of the LN, which could be cut into half (average, 9.8 LN patient), was examined by OSNA assay. Patients were classified in accordance with the UICC staging criteria and OSNA results, and the 3-year disease-free survival (DFS) of each cohort was analyzed.

Results: We enrolled 204 patients with CRC, excluded 9 patients, and analyzed 195 patients (stage I: n = 50, stage II: n = 71, stage III: n = 74). Of the patients with node-negative CRCs, only one was OSNA positive at stage I, and 11 were OSNA positive at stage II. OSNA-positive stage II cases had much lower 3-year DFS rate than OSNA-negative ones (p = 0.005). Among various clinical and pathological parameters, only OSNA status was a significant prognostic factor for 3-year DFS in stage II CRC cases (p = 0.025).

Conclusions: This prospective multicenter study showed for the first time a prognostic value of OSNA positivity in stage II CRC. This assay is useful for identifying at risk patients with stage II CRC. Further study to determine the treatment strategy for patients with OSNA-positive stage II CRC is necessary.

Legal entity responsible for the study: OICI

Disclosure: None

Impact of Immune response-associated gene polymorphisms on tumor response in rectal cancer patients treated with capецebitabine +/- oxaliplatin and radiation in the ACCORD-12/PRODIGE-2 phase III trial

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Background: We examined whether 133 germline polymorphisms (SNPs) in 15 candidate genes (CSF1R, IL8RA, IL1RA, IL1B, IL6R, IL10, IL10RA, IL15, IL1B, IL1RA, IFNGR1, IFNGR2, IL10, IL10RA, CTLA4, IL2, IL2RA, TGFβ1, ICOS, TLR4, CSF1R, IL8RA) were associated with tumor response to the ACCORD-12/PRODIGE-2 phase III trial which randomly compared neoadjuvant radiotherapy (RT) plus capецebitabine (CAP) with dose-intensified RT plus capецebitabine and oxaliplatin (CAPOX50) in T3-4 N0 M0 resectable rectal cancer.

Methods: A candidate-gene association study was conducted in 316 patients (n = 161 in the CAPOX50 and n = 155 in the CAP545 arm). The primary end-point was tumor response according to the Dworkor score in each arm. Logistic regressions were used to assess univariate/multivariate associations. The Storey and Tibshirani method based on the control of false discovery rate was used (q-value <0.10 considered as true discovery).

Results: Multivariate models adjusted on treatment arm were performed to determine prognostic and predictive values of haplotypes (R package SNSass and package haplo gm were used) for tumor response.

Results: In univariate analysis, two SNPs in IL15RA (rs11256456: OR = 5.1 [2.38, 11] and rs708761: OR = 4.2 [1.98, 8.74]) were significantly associated with the Dworkor score in the CAP45 arm, and one in IL8RA the CAPOX50 arm (rs1024396: OR = 0.11 [0.01; 0.90]). All were confirmed in the multivariate analysis. Patients were categorized into 3 haplotype groups after the haplotype analysis of IL15RA rs11256456 and rs708761: one had a positive prognostic effect on tumor response in the CAP45 arm (OR = 3.85 [1.97; 7.53], p = 0.0001) and in the overall population (OR = 1.76 [1.15; 2.68], p = 0.009). Interaction was also significant, suggesting a predictive positive effect of the same haplotype for response to CAP545 (OR = 4.12 [1.71, 9.94], p = 0.002).

Non of the three IL8RA SNPs were correlated with survival in the multivariate analysis.

Conclusions: This pharmacogenomic analysis shows that SNPs in IL15RA are significantly associated with response to neoadjuvant chemotherapy in patients with locally advanced rectal cancer. Their predictive effect may identify patients who benefit from CAP45.

Legal entity responsible for the study: UNICANCER

Disclosure: None

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Improved treatment decisions in colon cancer: The tumor-stroma ratio (TSR) additional to the TNM classification

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Background: The tumor-micro environment is an important determinant of patient behaviour. We developed a new, easy to apply, practice changing method to select
colorectal cancer patients for adjuvant therapy: the tumour-stroma ratio (TSR). This parameter is independently validated. The current proposal aims to prepare implementation of the method by training international pathologists and prospective validation of the parameter in an international setting.

Methods: 1. A reproducibility study on TSR scoring in H&E stained tissue samples will be conducted among international pathologists. An e-learning module will be developed with a quality assessment program in the framework of the European Society of Pathology EAOP program. 2. Automation of the TSR using whole slide imaging and state-of-the-art pattern recognition techniques. 3. A prospective clinical trial will be performed that evaluates the introduction of the TSR in clinical practice.

Results: A high amount of stroma within the primary tumor results in worse patient outcome. The TSR can be determined at routine pathology diagnostics and has an excellent inter-observer agreement with K \(> 0.80\). The TSR has been validated by independent international groups. Moreover it has been validated for breast, oesophageal, cervical, lung and gastric cancer. For colon cancer several cohort studies resulted in significant differences in survival between stroma-high and stroma-low patients (\(p < 0.0001\), HR 2.5). These results were validated in the VICTOR trial (stage II, III: OS \(p < 0.0001\), HR = 1.96, DFS P < 0.0001, HR = 2.15) and the Quasar II study (stage II, III: OS \(p = 0.083\), HR = 1.53, DFS \(p = 0.001\), HR = 1.53).

Conclusions: Standardization and prospective validation of TSR will result in inclusion of the parameter in the TNM classification leading to more accurate decision making for adjuvant therapy.

Legal entity responsible for the study: Leiden University Medical Center

Funding: Dutch Cancer Society (KWF)

Disclosure: All authors have declared no conflicts of interest.

Development and validation of multiplex biomarker assay to stratify colorectal cancer (CRC) patient samples into subtypes


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Background: We previously classified colorectal cancer (CRC) into five distinctive subtypes (CRCAsigner) and later into four consistent molecular subtypes (CMS) based on microarray or RNAseq gene expression profiles. The goal of this study was to develop a less expensive multiplex biomarker assay to stratify patient samples into CRC subtypes using the nCounter platform (NanoString Technologies) with short turn-around time for potential clinical use.

Methods: We used three cohorts of primary untreated CRC samples (n = 51) with two microarray (Del Rio, Montpellier Cancer Research Institute, France and OncoGene, Rockville, MD, USA) and one RNAseq (SG; Singapore General Hospital, Singapore) gene expression profiles. We reduced our published 786-gene CRCAsigner signature (CRCAsigner-786) into a short gene panel (CRC-panel). Initially, we compared CMS subtypes with CRCAsigner-786 subtypes, followed by CRCAsigner-786 subtypes with that of the microarray/RNAseq-based CRC-panel. We then developed a customized nCounter CRC-panel compared to different subtype classifications. To assess reproducibility, we generated technical replicates.

Results: There was an average of 70% concordance between CMS and CRCAsigner subtypes across different cohorts. 94% of predicted subtypes were concordant using microarray (Del Rio, Del Rio) and CMS criteria. In the 3 cohorts, nCounter CRC-panel classified 82% (74/91) of Del Rio and 65% (11/17) of OncoGene samples consistently with microarray-based CRC-panel classification. In the 2 cohorts, nCounter CRC-classified samples (76% 113/147) 17% and 14% (16/117) of samples consistently with RNAseq CRCAsigner and RNAseq CRC-panel, respectively. Pearson’s correlation coefficient between five pairs of technical replicates was 0.98.

Conclusions: nCounter assay stratified CRC samples into subtypes to known classifications. Given the high reproducibility and reduced costs, nCounter platform has been tested in formalin-fixed paraffin-embedded samples (ESMO-2017 Abstract-#3467). This assay may facilitate prospective validation of CRC subtypes in the clinic.

Legal entity responsible for the study: Institute of Cancer Research (ICR), London

Funding: NIHR Biomedical Research Centre

Disclosure: A. Sadanandam: Entitled to a share of royalties received by the licensor for a patent number PCT/IB2013/060416 in colorectal cancer subtypes. Research funding from Bristol-Myers Squibb for pancreatic cancer. All other authors have declared no conflicts of interest.

HER2 overexpression and amplification in patients with colorectal cancer (HOLIC): A large-scale retrospective study in Chinese population

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Background: HER2 overexpression or amplification may be a potentially predictive factor for anti-HER2 response and anti-EGFR resistance in colorectal cancer (CRC). However, the prevalence of HER2 positivity in CRC patients and its correlation with clinicopathologic features are not clear.

Methods: HER2 and MMp protein expression were tested by immunohistochemistry (IHC) in formalin-fixed, paraffin-embedded samples from 4,913 consecutive CRC patients treated with surgical resection during 2011-2014 in our institution. Dual color silver-enhanced in situ hybridization (DISH) was performed in all IHC 3+2+ cases. The scoring criteria of HER2 status in gastric cancer was used. RAS/BRAF mutation status was assessed by Sanger DNA sequencing.

Results: HER2 positivity was found in 160/4,913 (3.3%) cases, including 68 cases (42.5%) with IHC 3+ and 92 cases (57.5%) with IHC 2+DISH+. HER2 positivity was more common in younger patients and in tumors with high Ki67, vascular invasion, lymph node metastases, and higher TNM stage. HER2 positivity was not related to tumor location. Only one HER2 positive case had MMR protein deficiency. Among the 160 HER2 positive cases, 56 (35%) harbored a KRAS mutation, 17 (10.6%) harbored a NRAS mutation, and 4 (2.5%) harbored a BRAF mutation.

Conclusions: To our knowledge, this is the largest study of HER2 status in Asian patients with CRC. HER2 positivity occurred in a small number of patients with CRC, related to unfavorable prognostic factors, more common in younger patients and rare in MMR deficiency cases. Compared with previous results in western population, the RAS/BRAF mutation rate of HER2 positive Chinese CRC patients seems much higher. The further study regarding molecular information of these HER2 positive CRC patients is ongoing.

Legal entity responsible for the study: Fudan University Shanghai Cancer Center

Funding: None

Disclosure: All authors have declared no conflicts of interest.

The inflamed immune phenotype can be induced by systemic treatment in angiogenic colorectal liver metastases in contrast to non-angiogenic liver metastases


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Background: Recent data suggest that patients with colorectal cancer who present with desmoplastic (angiogenic) histopathological growth pattern (HGP) colorectal liver metastases (CLM) might derive more benefit from bevacizumab-based chemotherapy than patients who present with replacement (non-angiogenic) HGP CLM.

Methods: The immune phenotype (“inflamed”, “excluded”, “desert”) was analyzed regarding the association with HGP in a cohort of 118 patients with resectable CLM (n = 66:52, median age 62.3 (31.0-80.4) years, median follow-up 32.2 (5.0-92.7) months treated with 3 months of neoadjuvant and adjuvant bevacizumab-based chemotherapy and liver resection. The HGPS of CLM were assessed on H&E-stained sections according to international guidelines. The immune phenotypes were based on the distribution pattern of cytotoxic T lymphocytes in CD68-immunostained tissue sections.

Results: In 39.8% of the lesions the predominant means of vasculization was vessel co-option, as reflected by the replacement HGP. This non-angiogenic growth was associated with worse recurrence-free and overall survival (RFS, OS) with hazard ratios (HR) of 2.03 and 2.63 (P = 0.002 and P = 0.005, respectively). The HGPS were associated with the immune phenotypes. About 60% of the desmoplastic (angiogenic) HGP CLM were “inflamed”, while this was true for only 17% of the replacement (non-angiogenic) HGP CLM. More than half of the CLM with non-angiogenic growth were characterized by an immune desert as opposed to only 6% of the angiogenic CLM (P = 0.001). The non-inflamed immune phenotypes were associated with worse RFS (HR 1.85; P = 0.03).

Conclusions: Immune regulatory and angiogenesis pathways are known to interact. Our data suggest that the inflamed immune phenotype can be induced by systemic treatment in angiogenic CLM. The HGPS therefore are a potential biomarker for treatment that includes targeting the immune contexture.

Legal entity responsible for the study: Heinz-Josef Lenz

Funding: NIH

Disclosure: H-J. Lenz: Consulting or advisory role, Bayer, Novartis, Merck KG, Genentech/Roche, Boehringer-Ingelheim. Research funding: EMD, Bayer, BMS.
Whole-exome sequencing of matched germline and cell-free DNA portrays the somatic mutation landscape of refractory metastatic colorectal cancer and identifies mutated KDR/VEGFR2 as new cause of therapy resistance

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Background: Anti-angiogenic therapies have been broadly used in oncology as in treat-ment of metastatic colorectal cancer (mCRC) patients, however the causes of resistance occurring in the majority of the patients treated remain largely unknown.

Results: We investigated a RAS/BRAF/PIK3CA wild-type mCRC patient highly refractory to (sequentially): FOLFIRI-ctuximbab, FOLFOX-bevacizumab, afatin-ctuximbab (phase-1 trial), oncolytic adenovirus monotherapy (phase-1 trial), capcitabine-bevacizumab and fi-nally regorafenib. No radiological or clinical benefit was observed after any of these treat-ments and the patient died due to his progressive disease within 14 months. WES-gDNA enabled us to identify the KDR/VEGFR2 L840F mutation exclusively in the cancer sample. Using the most comprehensive experimental data showing that L840F decreases efficiency of TKIs, promote tumor growth and confer strong in vivo resis-tance to numerous anti-angiogenic therapies, including bevacizumab and VEGFR2 inhibi-tors. Other BEK/FR2 somatic mutations we retrieved from cancer sequencing projects showed similar oncogenic and resistant phenotype.

Conclusions: Our study introduces WES-gDNA as a robust noninvasive gene discover-y platform capable of portraying the somatic mutation landscape of metastatic cancer pathy from blood sample solely. Moreover, we cultured a previously unexpected oncogenic and cancer therapy modulating role of VEGFR2 mutants.

Legal entity responsible for the study: Rodrigo Toledo, Manuel Hidalgo

Funding: None

Disclosure: All authors have declared no conflicts of interest.

The nationwide colorectal cancer screening project in Japan, SCRAM-Japan GI-SCREEN: Identifiable efficient cancer gene alterations in advanced colorectal cancer

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Background: We initiated the Nationwide Cancer Genome Screening Project in Japan since February 2014. From February 2015, we have introduced the Next Generation Sequencing to detect cancer genome alterations in advanced colorectal cancer (aCRC), called as the SCRUM-Japan Gi-SCREEN. The objective is to evaluate the frequency of cancer genome alterations and to identify patients who are candidate for clinical trial with corresponding target agents.

Methods: This study is ongoing with 20 major cancer centers. Patients with aCRC who plan to or receive chemotherapy were eligible. DNA and RNA were extracted from formalin-fixed paraffin embedded (FFPE) tumor samples and were analyzed by the Oncomine Cancer Research Panel (OCR) which allows to detect mutations, copy number variant (CNV) and fusion genes in a CLIA certified CAP accredited lab. The de-tected genomic variant data were classified according to genetic drivers of cancer, including gain- and loss-of-function or single nucleotide variant based on the Oncomine Knowledgebase.

Results: As of October 31st in 2016, total of 1011 aCRC patients were enrolled and 981 samples were analyzed. The sequence was successfully performed in 751 tumors (76.6%). Out of 751 patients, the origin of samples included the primary site of 83.1% (Right-side 24.6%, Left-side 58.5%), metastatic site of 15.3%, and unknown of 1.6%. The frequently detected mutations in 751 samples of which results were available were TP53 (69.5%), APC (62.8%), KRAS (43.8%), and CNVs (> 2 copies) were FLT3 (3.6%), ERBB2 (2.8%), and MYC (2.7%). BRAF V600E was identified in 48 cases (6.4%) and CCDC6-RET fusion was identified in one case (0.1%). We will show the clinical outcome based on certain key cancer genome alterations.

Conclusions: This nationwide screening system is efficient to detect rare gene alter-ations in aCRC. This novel knowledge provides an intriguing background to investigate new targeted approaches in these patients and represents the progress toward precision medicine.

Clinical trial identification: UMIN000016343, 2015/01/26

Legal entity responsible for the study: SCRAM-Japan GI-SCREEN

Funding: 15 SCRAM-Japan collaborating pharmaceutical companies, AMED, NCC


Clinical utility of quasi-monomorphic variation range (QMVR) on the determination of microsatellite instability (MSI) status in patients (pts) with colorectal cancer (CRC): GI-SCREEN CRC-MSI sub-study 01

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Background: The current analysis for the determination of Microsatellite Instability (MSI) status using DNA markers matched normal DNA as references. Five quasi-monomorphic markers (NR-21, BAT-26, BAT-25, NR-24, and MONO-27) of the Promega panel are known to have few variant alleles in both Caucasian and Asian patients. For that reason, the peak of PCR products from normal DNA are confined within the Quasi-Monomorphic Variation Range (QMVR), of which Japanese pts with metastatic colorectal cancer (mCRC) are almost the same as those of Caucasian (Patil DT, et al., 2012 and Bando H. ASCO-GI 2017).

Methods: The purposes of this clinical evaluation study are to establish the QMVR in Japanese pts with mCRC and to evaluate the clinical utility of the QMVR in the determination of MSI status without matched normal DNA. The primary endpoint is the concordance of MSI status between the standard method using DNA from tumor plus matched normal samples and testing method using DNA from only tumor samples.
The new MSI kits including the Promega MSI panel were manufactured under the Quality Management System (QMS) for in vitro diagnostics (IVDs). As the decision algorithm, tumors exhibiting 2 or more markers outside the QMVR were classified as MSI-H, cases with 1 marker or without any marker outside the QMVR were classified as non MSI-H (MSI-L/MSI-).

Results: Totally 435 pts with mCRC were enrolled. Median age was 66 years old and 248 (57.09%) pts were male. 368 (84.60%) patients were primary and 67 (15.40%) metastatic specimens were used. There were 11 (2.5%) MSI-H cases by the standard method and the sensitivity of the testing method was 100% while the specificity of the testing method was also 100%. Thereby the two methods was completely concordant. Among the five quasimonomorphic markers, 3 and 2 cases were discordant in NR-21 and BAT-25, respectively. In BAT-26, NR-24, and MONO-27, all cases were completely concordant.

Conclusions: By using the QMVR, MSI status of Japanese pts with mCRC can be determined without matched normal DNA; and the QMVR might be applicable to Caucasian pts.

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Legal entity responsible for the study: FALCO Biosystems Co., Ltd.

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568P The impact of antiangiogenic therapy on intrahepatic colorectal cancer screening
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Background: The impact of antiangiogenic therapy on intrahepatic colorectal cancer (CRC) screening in the general population remains unclear.

Methods: A prospective cohort of patients undergoing endoscopy with positive iFOBT in 2015 at 3 centers in Belgium was analyzed. Medical records were reviewed for demographic and clinical variables: gastro-intestinal (GI) symptoms, family history of polyps/CRC, use of antithrombotics (including aspirin and/or Clopidogrel), Dipyridamole, Ticagrelor, novel anticoagulants or vitamin K antagonists. Endoscopy reports were checked for colorectal pathology. Significant findings were defined as CRC or advanced adenomas. Rates of false positive iFOBT and detection of CRC or advanced adenomas were compared in patients with and without antithrombotics or aspirin. Finally a distinction was made between patients who had a iFOBT through programmatic or opportunistic screening.

Results: A total of 530 patients (64% male, median (IQR) age 63.2 years) with positive iFOBT were included. Colorectal pathology was confirmed in 73% of the patients; more commonly in males and family history. Significant findings were present in 220/371 (59%) patients with colorectal pathology. Antithrombotics were used in 23% of the patients and associated with male gender, older age and lower GI symptoms. Aspirin alone was used in 17% and associated with male gender and older age. Rates of false positive iFOBT, detection of advanced adenoma and CRC were similar in patients with or without antithrombotics and in patients with Aspirin alone compared to no antithrombotics. iFOBT was mainly used in programmatic screening (91%), with no differences in demographic or clinical variables between these two groups.

Conclusions: Although antithrombotic drugs were mostly prescribed in male and older patients with an inherent higher cancer risk, detection rates of CRC and advanced adenoma’s were similar. Despite the higher rate of lower GI symptoms, antithrombotics or aspirin alone did not lead to more false positive iFOBT. Use of antithrombotics or Aspirin alone does not seem to impact the performance of iFOBT for screening of CRC in the general population.

Legal entity responsible for the study: OLV Aalst

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Disclosure: All authors have declared no conflicts of interest.

569P miR-93 regulates epithelial-to-mesenchymal transition process in metastatic colorectal cancer by targeting EphA4
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Background: Regulating epithelial-to-mesenchymal transition (EMT) in cancer cells has been widely considered as an approach to combat cancer progression and therapeutic resistance, whereas a limited number of broadly comprehensive investigations of miRNAs involved in metastatic colorectal cancer (mCRC) have been conducted. In this study, we investigated the roles and mechanisms of EMT process in mCRC.

Methods: We used in situ hybridization and quantitative reverse transcriptase polymerase chain reaction to measure expression of miR-93 in colorectal tissues, nontumor tissues and metastatic liver tissues. CRC cell lines were transduced with lentiviruses that expressed miR-93, or scrambled targeted miR-93 or a scrambled sequence (control); proliferation, metastasis, invasion and colony formation were analysed. We analysed growth of CRC cells that overexpress miR-93 or its inhibitor in severe combined immune-deficient mice. Western blot, and luciferase reporter assays were used to measure expression and activity of Eph tyrosine kinase receptor (EphA4) and related signalling molecules.

Results: In this study, we demonstrated that miR-93 regulated the epithelial-mesenchymal transition (EMT) process by targeting EphA4 in metastatic colorectal cancer (mCRC). We examined the fact that CRC tissues and metastatic liver tissues had increased levels of miR-93 compared with the nontumor tissues and cells, by which we identified miR-93 can regulate EMT process. In addition, overexpression of miR-93 increased proliferation of CRC cells, metastasis, invasion and colony formation in vitro, whereas miR-93 depletion reduced these parameters. In severe combined immune-deficient mice, overexpression of miR-93 by CRC cells increased liver metastasis and overexpression of the miR-93 inhibitor reduced it. By further study the role of miR-93 on proliferation, migration, invasion and liver metastasis in CRC cells.

Conclusions: Our findings for the first time revealed that miR-93 regulates the epithelial-mesenchymal transition (EMT) process by targeting EphA4 to affect liver metastasis in colorectal cancer (CRC). Mechanistically, miR-93 inhibited tumor metastasis by directly targeting EphA4 which is a crucial factor in regulating EMT. Collectively, this study provide new insights into exploring the therapeutic potential of miR-93 which is able to regulate EMT process to affect tumor metastasis, and warrant further study in clinical settings.

Clinical trial identification: The present study was supported in part by grants from the Health and Family Planning Commission of Shanxi Province (No 2015049), the Applied Basic Research Programs of Shanxi Science and Technology Department (No.201610D011128)

Legal entity responsible for the study: Department of Colorectal Cancer, Shanxi Cancer Hospital and Institute

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Disclosure: All authors have declared no conflicts of interest.

570P Array based profiling of emerging molecules in colorectal cancer
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Background: Colorectal cancer (CRC) also has various genetic backgrounds and diversity. In addition to the RAS gene, a lot of new knowledge about molecules playing an important role in the process of carcinogenesis or drug resistance, and emerging molecules as targets for new treatments have been reported recently. In this research, we aim to clarify correlation between emerging molecules and differences through clinical stages in CRC using tissue array.

Methods: Consecutive patients who underwent surgery in our hospital from June 2003 to March 2011 were enrolled in this study. Tissue array based profiling of emerging molecules was performed on archival samples using immunohistochemistry for MLH1/MSH2/MSH6/PMS2, CDX2, HER2 and PD-L1, and fluorescence in situ hybridization for ERBB2. We analyzed the correlation among molecular profile, overall survival, pathological findings and location of CRC.

Results: A total of 1122 CRC from stage 0 to IV were analyzed; details in Table. In dMMR population, the proportion of PD-L1 expression (19.2%) was increased significantly compared to those in pMMR population (2.5%). In the univariate analysis, CDX2 negative, BRAF mutation and poorly differentiated histology and in the multivariate analysis, CDX2 negative, dMMR and poorly differentiated histology were identified as predictive factors for OS in whole population.

Conclusions: Our data comprehensively summarized the significance of the recent emerging molecules in CRC over the clinical stages. These are considered to contribute to precision medicine in near future.

Legal entity responsible for the study: Ethical Guidelines for Medical Research on Humans

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Disclosure: E. Shinozaki: Honoraryaria from Taiho, Merck Serono, Chugai, Yakult, Ono, Takeda, Bayer and Lilly. All other authors have declared no conflicts of interest.
Background: The implementation of CRC subtypes along with other molecular features in clinic is challenging due to lack of easy-to-use and low cost assays suitable for FFPE issues. Based on our CRCAssigner and Consensus Molecular Subtype (CMS), we validated a small gene panel for nCounter assay (Nanostring Technologies) to classify CRC fresh-frozen samples (Esmo 2017 Abstract 4633). Here, we tested nCounter and MiSeq platforms (Illumina; targeted mutational panel) in archival FFPE samples.

Methods: Tissues from 36 chemoradiotherapy patients treated at the Royal Marsden were collected. Tumour-enriched areas were microdissected, RNA/DNA was extracted, and nCounter assay was performed. RNA technical (same extraction, n = 6) and biological (same block, different extractions, n = 3) replicates were generated. Hotspot BRAF, KRAS, NRAS, PIK3CA, TP53 mutations (MT) were sequenced.

Results: Out of 26 untreated primaries, 8 were enterocyte/transit-amplifying (TA) (CMS2, 30%), 7 goblet-like (CMS3, 27%), 8 stem-like (CMS4, 30%), 0 inflammatory (CMS1, 30%), 3 TA (CMS2, 30%), 3 stem-like (CMS4, 30%), and 1 mixed subtypes. Pearson correlation coefficients were 0.96 and 0.88 (high reproducibility) for technical and biological replicates, respectively.

Conclusions: With the caveat of small numbers, the subtype distribution in chemoradiotherapy patients is different compared to early stage patients assessed within the CMS consortium. The enrichment for less differentiated subtypes in pre-treated samples suggests potential treatment-induced changes in tumours. Overall, nCounter assay along with MiSeq platform was able to classify standard archival diagnostic CRC FFPE samples into subtypes, which warrants further improvement and validation for clinical practice.

Legal entity responsible for the study: The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research

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Disclosure: D. Cunningham: Research funding to institution: Amgen, AstraZeneca, Bayer, Colgene, MedImmune, Merck Serono, Merck KGaA, Novartis, Sanofi. I. Chau: Research funding: Janssen. C. Peckitt: Advisory roles with Sanofi. D. Watkins: Funding for meeting attendance from Amgen. I. Chau: Honoraria: Amgen, Bayer, Pfizer, Taiho Pharmaceutical. Consulting or advisory role: Bristol-Myers Squibb, Gilead Sciences, Lilly, Merck Serono, MSD, Sanofi. Research funding: Janssen-Cilag, Merck Serono, Novartis, Roche, Sanofi. N. Starling: Research funding to institution: AstraZeneca, Verastem. A. Sadanandam: Entitled to a share of royalties received by the licensor for a patent application number PCT/IB2013/056416. Research funding from Bristol-Myers Squibb for pancreatic cancer. All other authors have declared no conflicts of interest.
Background: Microsatellite instability (MSI) is one of the most important prognostic factors in patients with colon cancer but the impact of MSI in rectal cancer, which is known to have a lower incidence of MSI-high (MSI-H) tumours than proximal colon cancer, has not been fully evaluated. We studied whether MSI status affects survival in stage II and III rectal cancer patients who underwent upfront curative resection.

Methods: 1138 patients who had operation between February 2008 and August 2015 in a single tertiary care center in South Korea were included and PCR-based MSI testing was performed on tumour tissue from each patient. Study endpoints were disease free survival (DFS) and overall survival (OS).

Results: Among 1138 patients, 25 (2.2%) had MSI-H tumours. Compared with microsatellite stable (MSS) or MSI-low (MSI-L) tumours, MSI-H showed similar clinical characteristics including age at diagnosis, gender, tumour location and pathologic tumour stage but they were highly associated with histological grade of tumour (p = 0.005) and presence of family history of colorectal cancers (p = 0.003). The 5-year DFS rates for patients with MSI-H and MSS/MSI-L were 78.0% and 69.2%, respectively (p = 0.637), and the 5-year OS rate was 84.0% with MSI-H and 82.4% with MSS/MSI-L (p = 0.735). In multivariate Cox regression analysis, there was also no significant difference in either DFS (p = 0.855) or OS (p = 0.912) for the patients with rectal cancer based on MSI status.

Conclusions: Our results suggested that MSI has no definite prognostic role in patients with rectal cancer. MSI status was associated with differentiation of tumour and family history of colorectal cancer.

Legal entity responsible for the study: Department of Oncology, Asan Medical Center, Seoul, Republic of Korea

Funding: None

Disclosure: All authors have declared no conflicts of interest.

577P

EXOMAL ECM1 PROTEIN EXPRESSION IN PLASMA FROM THE TUMOR-DRAINING VEIN (MESENTERIC VENOUS) AND TIME TO RELAPSE IN COLON CANCER PATIENTS

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Background: Exosomes are microvesicles that contain and transport coding and non-coding RNA, DNA, and proteins. They are secreted by several cell types, including...
tumor cells, and captured by receptor cells in a target organ, where they modify the tissue microenvironment, forming a pre-metastatic niche where circulating tumor cells can anchor. It has recently been found that blood from a tumor-draining vein can provide more reliable information about biomarkers than that obtained from a peripheral vein (PV). Venous return from the colon occurs through the mesenteric vein (MV), making the MV an excellent source to analyze potential biomarkers contained in exosomes released by the tumor cells in colon cancer before they reach the target organ. We have assessed the presence of exosomal proteins in the MV and PV of surgically resected colon cancer patients and correlated our findings with time to relapse (TTR).

Methods: On the day of surgery, blood samples were obtained from the MV and PV of 31 stage I-III colon cancer patients. Exosomes were isolated by ultracentrifugation and confirmed by cryogenic transmission electron microscopy. High-throughput proteomic analysis by mass spectrometry was used to identify expression levels of exosomal proteins. Findings were confirmed by western blot in MV and PV samples, as well as in samples from healthy controls, using TSG101 as a recognized marker of exosomes.

Results: TSG101 was more highly expressed in relapsed patients than in non-relapsed ones or controls. The ECM1 protein was more highly expressed in both MV and PV exosomes in patients with relapse than in those from controls. However, ECM1 expression was 13 times higher in relapsed than in non-relapsed patients in MV – but not PV – exosomes. Among 17 patients with low exosomal ECM1 levels in MV, TTR was 40.2 months, compared to 31.3 months for 14 patients with high levels (P = 0.04).

Conclusions: A high ECM1 expression in MV exosomes is associated with poor prognosis in patients with metastatic instability high colon cancer.

Legal entity responsible for the study: University of Barcelona

Funding: None

Disclosure: All authors have declared no conflicts of interest.

**578P**

LAG-3 expression in tumor infiltrating immune cells is associated with poor prognosis in patients with microsatellite instability high colon cancer

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Background: Recent findings demonstrated that microsatellite instability high (MSI-H) colon cancer contains high T-cell infiltration and highly upregulated expression of multiple immune checkpoints. There is increasing evidence on the role of LAG-3 in the downregulation of T cell responses and on its involvement in tumor-infiltrated T regulatory function. The aim of this study was to reveal the prognostic impact of MSI-H colon cancer showing immune checkpoint protein expression, which are good candidates for immunotherapy.

Methods: From January 2011 to April 2015, we included 48 patients with MSI-H colon cancer who underwent curative surgery at Kyungpook National University Medical Center. Inhibitory receptors such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), lymphocyte-activation gene 3 (LAG-3), programmed death-ligand 1 (PD-L1), programmed cell death 1 (PD-1) and indolamine 2′-3′-dioxygenase (IDO) expression status were retrospectively analyzed using immunohistochemistry (IHC). Positivity in tumor cells (T) and immune cells (I) were separately evaluated. IHC values were determined to be positive when moderate or strong intensity of the membranous expression status were retrospectively analyzed using immunohistochemistry (IHC). Positivity in tumor cells (T) and immune cells (I) were separately evaluated. IHC values were determined to be positive when moderate or strong intensity of membranous

Results: Among the 48 patients, 22 patients (30.1%) demonstrated co-expression of LAG-3 and PD-L1, while 12 (31.0%) and 42 (56.2%) were determined as IDO (T) and IDO (I) positive, respectively. The median follow-up time was 13.3 months (95% CI, 11.5–19.4). The response rate and the rate of early tumor shrinkage were respectively 73.9% and 71.0%, achieving R0 resection rate of 24.6%. The major grade 4 neutropenia and FN were 13% and 10% (P = 0.0044 and P = 0.127). However, no association in terms of efficacy between UGT1A1 single heterozygous and wild-type pts was indicated.

Conclusions: The efficacy of FOxlQOXIRI plus Bevacizumab in Japanese were consistent with those of previous phase II and III studies in Asian patients with metastatic colorectal cancer. A prospective single-arm, multicenter, phase II study investigating the efficacy and safety of Japanese pts was conducted. A high ECM1 expression in MV exosomes was associated with poor prognosis in patients with MSI-H colon cancer.

Legal entity responsible for the study: Kyungpook National University Medical Center

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Background: The expression of interleukin 17 receptor A is associated with poor prognosis in patients with colorectal cancer and its knockdown inhibits tumor growth and modulates tumor-infiltrating immune cells in mice.

Methods: A number of RAS mutations confer resistance to anti-EGFR treatments used in the management of colon cancer. The objective of this study was to evaluate the ability of cell-free plasma DNA (cfDNA) to reflect the mutational status of a tumor in normal tissues of CRC patients by using quantitative RT-PCR and immunohistochemistry. To investigate the functional significance of IL17RA expression, and clinical significance of IL17RA expression in CRC patients, disease-free survival was analyzed in patients with CRC. The IL17RA knockdown stable clones were used for in vitro migration/invasion assay and were subcutaneously implanted in mice to measure tumor growth.

Results: A higher IL17RA mRNA level in tumor tissue of CRC patients than adjacent normal tissues (p = 0.0016) was found and it was significantly correlated with recurrence (r = 0.038) and poor disease-free survival (P < 0.001). The knockdown of IL17RA affected the tumor microenvironment and decreased tumor volume of subcutaneous xenograft model. The scarcity of IL17RA were found to inhibit the percentage of intratumoral tumor-infiltrating leukocytes including CD4+ CD25+ regulatory T cells and myeloid-derived suppressor cells as determined by flow cytometry analysis. Moreover, IL17RA knockdown cells increased apoptotic ability via upregulating PARP1, cleaved-caspase 3.

Conclusions: IL-17RA participates in mediating tumor growth and angiogenesis of CRC and plays a crucial role in the progression of CRC. It could serve as prognostic marker of CRC patients and could potentially be used as a therapeutic target in clinical application.

Legal entity responsible for the study: Chih-Yung Yang

Disclosure: All authors have declared no conflicts of interest.

Comparison of performances of three technologies for detection of RAS mutations in cfDNA (NGS strategy, BEAMing assay and ddPCR BioRad assay)

Backgound: A number of RAS mutations confer resistance to anti-EGFR treatments used in the management of colon cancer. The objective of this study was to evaluate the ability of cell-free plasma DNA (cfDNA) to reflect the mutational status of a tumor in order to use liquid biopsies instead of invasive and painful solid tumor biopsies when monitoring tumor progression.

Methods: We selected tumors from the CIRCAN, a cohort. The molecular profiles from solid biopsies were routinely assessed with the PGM NGS technology. Plasma samples were collected at diagnosis (colon cancer) and during progression (lung cancer). KRAS and NRAS somatic alterations were quantified using three different technologies: droplet digital polymerase chain reaction (ddPCR) from BioRad and BEAMing (Oncombeam) from Symex Innomics, as well as next generation sequencing (NGS, NextSeq500) by Illumina) using the library prepared with the S6G oncology panel kit from Swift Biosciences.

Results: The highly sensitive and specific assays enabled us to obtain excellent matches with solid biopsies detected in cfDNA for colon cancer at diagnosis and for lung cancer during disease progression. When examining cfDNA from patients displaying mutations in their colon biopsy for one of the KRAS and/or NRAS mutations, 100% of the mutations were confirmed using the Oncombeam technology, whereas only 66% matched the initial PGM status using the two other technologies. The BEAMing technology enabled us to detect KRAS mutations in patients with negative biopsy, increasing the detection of the KRAS positive profiles compared to the standard solid biopsy method. cfDNA was sampled during progression and the high sensitivity and reproducibility of the BEAMing technology enabled us to identify patients with KRAS persistence and others, developing an additional mechanism of relapse.

Conclusions: The advantage of the NGS technology is the larger coverage of longer gene regions for screening purposes, while the BEAMing technology provides highly sensitive results allowing us to follow the kinetics of appearance and disappearance of somatic alterations, linked to the efficiency of therapies.

Legal entity responsible for the study: Hospices Civils of Lyon

Funding: AstraZeneca, Symex, Merck

Disclosure: All authors have declared no conflicts of interest.

The expression of interleukin 17 receptor A is associated with poor prognosis in patients with colorectal cancer and its knockdown inhibits tumor growth and modulates tumor-infiltrating immune cells in mice.

Background: Interleukin 17 receptor type A (IL17RA) is a potent mediator in the pathogenesis and progression of colorectal cancer. Our previous study has shown that IL17A is a potential therapeutic target in modulating tumorigenesis, and metastasis, and serves as a prognostic marker in colorectal cancer (CRC), but the role of IL17RA in colonic tumorigenesis is still not clear. This study aims to evaluate the potential role and function of IL17RA in CRC.

Methods: IL17RA expression was determined in colorectal cancer tissues and adjacent normal tissues of CRC-patients by using quantitative RT-PCR and immunohistochemistry. To investigate the functional significance of IL17RA expression, and clinical significance of IL17RA expression in CRC patients, disease-free survival was analyzed in patients with CRC. The IL17RA knockdown stable clones were used for in vitro migration/invasion assay and were subcutaneously implanted in mice to measure tumor growth.

Results: A higher IL17RA mRNA level in tumor tissue of CRC patients than adjacent normal tissues (p = 0.0016) was found and it was significantly correlated with recurrence (r = 0.038) and poor disease-free survival (P < 0.001). The knockdown of IL17RA affected the tumor microenvironment and decreased tumor volume of subcutaneous xenograft model. The scarcity of IL17RA were found to inhibit the percentage of intratumoral tumor-infiltrating leukocytes including CD4+ CD25+ regulatory T cells and myeloid-derived suppressor cells as determined by flow cytometry analysis. Moreover, IL17RA knockdown cells increased apoptotic ability via upregulating PARP1, cleaved-caspase 3.

Conclusions: IL-17RA participates in mediating tumor growth and angiogenesis of CRC and plays a crucial role in the progression of CRC. It could serve as prognostic marker of CRC patients and could potentially be used as a therapeutic target in clinical application.

Legal entity responsible for the study: Chih-Yung Yang

Disclosure: All authors have declared no conflicts of interest.

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Conclusions: IL-17RA participates in mediating tumor growth and angiogenesis of CRC and plays a crucial role in the progression of CRC. It could serve as prognostic marker of CRC patients and could potentially be used as a therapeutic target in clinical application.

Legal entity responsible for the study: Chih-Yung Yang

Disclosure: All authors have declared no conflicts of interest.
Background: Until now, we have managed all CRC patients (pts) in the same way. However, emergent data show that left division of primary tumor can have a prognostic and predictive value in metastatic setting. In this study, we analyzed differences in survival between right (R) and left-sided (L) CRC.

Methods: This prospective, multicentre observational study was conducted in coordinating with 22 public-sector hospitals of Spain. Pts diagnosed with new CRC, stage IV and surgically treated, were included. We defined R-CRC as tumors originated in cecum, ascending colon, hepatic flexure or transverse colon, and L in splenic flexure, descending and sigmoid colon or rectum.

Results: Of 2624 recruited pts, 807 (30%) had R and 1887 (70%) L-CRCs. Most of cases were non-metastatic (89%), and males (63.5%). Mortality risk was higher for R-CRC and independent of stage (localised vs metastatic), with HR 1.69, 95% CI 1.24-2.29. Pts with R-tumors were slightly older than L, with a higher Body Mass Index (BMI), a greater predominance of women, non-smokers and regular Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) users. At presentation, they stayed asymptomatic, had more frequent vascular invasion, and primary tumor location. Cecum to transverse colon classified as right-sided CRC (R-CRC), splenic flexure to rectum classified as left-sided CRC (L-CRC).

Conclusions: Pts with R-CRC were more likely to be older, with higher BMI, a greater proportion of women, non-smokers and regular NSAIDs users. Some of pts with R-CRC showed more vascular invasion, and primary tumor location. Cecum to transverse colon classified as right-sided CRC (R-CRC), splenic flexure to rectum classified as left-sided CRC (L-CRC). R-CRC pts had a higher mortality risk compared to L-CRC pts.

Table: 858P Differences in survival and clinicopathological characteristics (cpc) between right and left-sided colorectal cancer (CRC): A CARESS-CCR group study

<table>
<thead>
<tr>
<th>Variable</th>
<th>R-CRC</th>
<th>L-CRC</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sv 2 years (%), 95% CI</td>
<td>87.9 (85.5 - 90.3)</td>
<td>91.9 (90.6 - 92.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>Age (mean, SD)</td>
<td>69.8 ± 10.5</td>
<td>67.8 ± 11.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Woman (%)</td>
<td>43.0</td>
<td>33.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (mean, SD)</td>
<td>28.1 ± 5.0</td>
<td>27.5 ± 4.7</td>
<td>0.008</td>
</tr>
<tr>
<td>Non-Smoker</td>
<td>55.4</td>
<td>45.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Regular NSAIDs user (%)</td>
<td>6.7</td>
<td>4.4</td>
<td>0.07</td>
</tr>
<tr>
<td>Asymptomatic (%)</td>
<td>10.5</td>
<td>7.5</td>
<td>0.017</td>
</tr>
<tr>
<td>Interval tumor (%)</td>
<td>12.3</td>
<td>7.1</td>
<td>0.038</td>
</tr>
<tr>
<td>Elevated Ca 19.9 (%)</td>
<td>18.8</td>
<td>13.5</td>
<td>0.029</td>
</tr>
<tr>
<td>Urgent surgery (%)</td>
<td>6.4</td>
<td>3.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mucinous, signet-ring and medullary (%)</td>
<td>16.5</td>
<td>7.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High grade (%)</td>
<td>20.1</td>
<td>10.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vascular invasion (%)</td>
<td>18.7</td>
<td>11.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T stage</td>
<td>T1-T2</td>
<td>19.5</td>
<td>29.2</td>
</tr>
<tr>
<td>T3-T4</td>
<td>80.1</td>
<td>67.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Conclusions: R and L-CRCs are different, and prognosis is better for L-tumors, independently of stage.
**586P The prognostic value of sidedness of the primary tumor after local treatment for oligometastatic colorectal cancer: A Danish population based study**

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Background: Metastasis directed therapy of metastatic colorectal cancer (mCRC) includes resection, radiofrequency ablation (RFA) and stereotactic radiotherapy (SBRT) of liver and/or lung metastases. The location of the primary tumor may influence survival in advanced disease. The aim of this study was to analyze the prognostic value of the primary tumors sidedness after local treatment of oligometastatic CRC in a national population based study.

Methods: Data was retrieved from the Danish Cancer Registry and the Danish National Patient Registry (DNPR) from all patients who underwent surgery for CRC between 2000-2013. Additional data from the DNPR included liver and/or lung metastases, RFA or SBRT. Based on the surgical codes for primary tumor resection in DNPR, patients were grouped as right or left sided (including rectal cancer). Survival was calculated from the date of last recorded treatment until death from any cause or end of follow-up. A Cox proportional hazard model was used to compute hazard ratios (HRs) for mortality between groups adjusting for age, gender, co-morbidity, nodal stage and site of local treatment.

Results: A total of 38131 patients had surgery for a primary CRC and 2912 patients underwent a total of 3662 metastasis directed procedures. The median age was 64.9 years (range 20-92 years) and 59% were male. Local treatment modalities comprised liver surgery (n = 1616), lung surgery (n = 1075), liver RFA (n = 705), liver SBRT (n = 124) and lung SBRT (n = 821). In the latter the data were evaluated separately. Of 2,264 patients were resected for a right and left primary sided tumor, respectively, (unknown primary location n = 58). For all patients (n = 2912), the median survival was 3.8 years (95% CI 3.6-4.0) for patients treated with RFA compared to the 3.2 years (95% CI 2.7-3.5) and 4.0 years (95% CI 3.8-4.2) for patients with left sided tumor. For patients with a right and left sided tumor, the median survival reached 3.2 years (95% CI 2.7-3.5) and 4.0 years (95% CI 3.8-4.2), respectively. As for the adjusted HR 1.20 (95%CI 1.07-1.38, p = 0.003).

Conclusions: In this national population based study, we report a longer median survival for CRC patients with a left sided primary as compared to right sided primary tumor after local treatment for liver and lung metastases.

Legal entity responsible for the study: Department of Epidemiology, Aarhus University Hospital

Funding: Aarhus University

Disclosure: A. Boysen: Advisory board: Bayer. All other authors have declared no conflicts of interest.

**587P Survival by sidedness of metastatic colorectal cancer (mCRC) treated with epidermal growth factor receptor antibodies (EGFR-Ab) in the refractory setting: A population-based study of 1509 patients**

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Background: Sidedness of primary is an established prognostic factor in mCRC and recently has been shown to be an important predictive factor for patients (pts) treated with EGFR-Ab (always in combination with chemotherapy) in 1st and 2nd line settings. Limited data is available in 3rd line and beyond, where EGFR-Ab are used either as monotherapy or with chemotherapy. In Ontario, Canada, public funding of EGFR-Ab is restricted to chemotherapy refractory disease. This study examines the impact of sidedness on overall survival (OS) in chemotherapy refractory mCRC treated with EGFR-Ab monotherapy and combination.

Methods: This population-based retrospective cohort study used linked data from the Institute for Clinical Evaluative Sciences to evaluate mCRC pts treated in Ontario with EGFR-Ab from Jan 2006-Dec 2014. Over 99% of cases are captured via the Ontario Cancer Registry. The primary outcome was OS. Monotherapy vs combination was compared by panitumumab (pani; funded only as monotherapy) v cetuximab (cet; funded only with chemotherapy) outcomes. Sidedness was determined by ICD-10 code as right (R; including transverse colon) or left (L).

Results: Of 16717 CRC pts,1553 received EGFR-Ab for refractory mCRC (429 R, 1080 L, 44 unknown). 71% received cetuximab. It was more commonly female, with significantly shorter time (months, m) from diagnosis to EGFR-Ab therapy (mean ± SD: 28.7 ± 18.3 v 32.8 ± 19.2, p < 0.001). Median OS for R with any EGFR-Ab therapy was significantly worse than L: 30.5 v 39.3 m (HR 1.22; 95% CI 1.07-1.38, p = 0.0026); this was true for monotherapy (HR 1.22; 95% CI 1.05-1.42, p = 0.0098) with a near-significant trend for combination (HR 1.30; 95% CI 0.99-1.7, p = 0.055). For L, OS was identical between monotherapy and combination. In R there was a near-significant trend to longer survival with combination (HR 0.76; 95% CI 0.58-1.01, p = 0.038).

Conclusions: This large population cohort demonstrates that R sidedness is significantly predictive for survival with EGFR-Ab in refractory mCRC, consistent with findings in earlier lines of therapy. The differences are particularly seen with monotherapy. L sided cancers appear to benefit equally from monotherapy as combination.

Legal entity responsible for the study: Monash University

Funding: None

Disclosure: All authors have declared no conflicts of interest.

**588P Differences in prescribing attitudes and treatment patterns between right-sided and left-sided mCRC in EU5 and the US**

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Background: There is evidence to suggest that location of primary colorectal tumours has an impact on prognosis and efficacy of biological agents. Studies focus on RAS WT (KRAS WT and NRAS WT) mCRC, and have identified that left sided colon cancer (LSCC) is more common than right sided colon cancer (RSCC). LSCC is associated more in males and is associated with a better prognosis. RSCC on the other hand, is observed more in females and is associated with a worse prognosis. Patients with LSCC show a better response to EGFR inhibitors, whereas those with RSCC show a better response to VEGF inhibitors. This study aims to demonstrate the differences in prescribing habits by tumour location in EU5 and US and to evaluate the impact of new clinical data on real-world treatment patterns.

Methods: Between July 2016 and January 2017, a panel of oncologists in EU5 (n = 624) and US (n = 101) were asked to report on mCRC RAS WT patients and their treatments through the submission of online de-identified record forms.

Results: Of 996 mCRC patients in EU5 and 821 in US, there are significantly more males with LSCC (57% & 56%) than RSCC (43% & 44%, p < 0.01), whereas for females the split between sides is not significantly different. Out of 2,106 1L RAS WT patients in EU5 and 198 in US, those with LSCC receive EGFR inhibitors more than RSCC (p = 0.01 & p < 0.05), but receive VEGF inhibitors less than RSCC patients (p < 0.01 EU5 only). There is no difference in treatment between LSCC and RSCC for 2L+ RAS WT patients in US, but in EU5 LSCC patients are prescribed VEGF inhibitors more than RSCC patients (p < 0.05). New clinical data is a more frequent reason for using VEGF inhibitors or chemo-only on RSCC (14% & 4%) than for LSCC (7% & 8%, p < 0.01) in EU5. In US, the same is true for chemo-only patients with RSCC (18%) compared to LSCC (4%), whereas ‘new clinical data’ is a more significant reason for using EGFR inhibitors on LSCC (14%) than for RSCC (0%, p < 0.01).

Conclusions: 1L mCRC patients with LSCC receive EGFR inhibitors more than RSCC patients, whereas RSCC patients receive VEGF inhibitors more than LSCC patients, a trend not observed in 2L+. This supports the literature when considering that ‘new clinical data’ has been a significant reason for these prescribing patterns.

Legal entity responsible for the study: Ipsos Healthcare

Funding: None

Disclosure: All authors have declared no conflicts of interest.

**589P Tumor sidedness and enriched gene groups for efficacy of 1st-line cetuximab (cet) treatment in metastatic colorectal cancer (mCRC)**


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Background: Primary tumor location (PTL) has been shown to be not only a prognostic factor but also predictive for 1st-line cet treatment in mCRC. Molecular differences

Disclosure: All authors have declared no conflicts of interest.
between PTLs may contribute the sidedness-specific response to cet. We investigated genes associated with efficacy of cet treatment depending on tumor sidedness.

**Methods:** We enrolled 77 patients (pts) (57% males, median 63.9-old, and 51% right-sided colon cancer) with KRAS exon 2 wild-type tumors from the JACCRO CC-05 or CC-06 trial of 1st-line therapy with cet plus FOLFOX or NOX, respectively. All pts’ tissues were measured for expression levels of 2500 genes by HTG EdgeSeq Oncology Biomarker Panel using next generation sequencing for quantitative analysis of targeted RNAs. Univariate Cox regression analysis using log2 values of counts per million (CPM) was conducted for all genes that passed QC filtering in each sidedness (left [L]/right [R]) to assess the association with clinical outcomes. Further univariate Cox regression analysis was performed to define an optimal cutoff point for significant genes. Also, we performed a gene set enrichment analysis (GSEA) to identify classes of genes associated with outcomes in each side. Tumors proximal or from L flexure to rectum were defined as R-sided or L-sided, respectively.

**Results:** Sixty of 77 pts were assessable for gene expression data. NOTCH1 high-expression (log2(CPM) ≥ 7.5) predicted significant longer progression-free survival (PFS) (median 14.7 vs. 11.1 m, HR 0.43, 95%CI 0.22-0.81, P = 0.01) and overall survival (OS) (median 62 vs. 26.5 m, HR 0.55, 95%CI 0.28-0.79, P = 0.01) in pts with L-sided tumor (n = 60) but not in R-sided tumor (n = 9). The GSEA showed that gene set of inflammatory response correlated with better PFS in both sides. The regulation of DNA replication gene set was associated with favorable OS but no gene set correlated with better PFS in both sides. Several types of gene set were identified to predict better or worse outcomes in R-side.

**Conclusions:** Our data suggest that gene expression signatures may explain differences in efficacy dependent on tumor sidedness. NOTCH1 may potentially discriminate favorable responders to cet in pts with L-sided tumors.

**Clinical trial identification:** UMIN000024594, Nov/24/2016

**Legal entity responsible for the study:** Japan Clinical Cancer Research Organization: JACCRO

**Funding:** Japan Clinical Cancer Research Organization: JACCRO


**Background:** This study was designed to evaluate the role of magnetic resonance imaging (MRI) on preoperative restaging locally advanced rectal cancer after neoadjuvant chemoradiotherapy (CRT), in order to facilitate individualization of surgical management.

**Methods:** We analyzed 106 patients who had received neoadjuvant CRT underwent a MRI before and after CRT. All patients underwent restaging MRI followed by surgery after the end of CRT. The primary endpoint of the present study was to estimate the accuracy of post-CRT MRI classification using pathologic staging.

**Conclusions:** MRI has low accuracy for restaging locally advanced rectal cancer after neoadjuvant chemoradiotherapy (CRT), in order to facilitate individualization of surgical management.
Quality of life in patients with liver metastases from colorectal cancer treated with first-line selective internal radiotherapy (SIRT): Results from the FOXFIRE prospective randomized studies

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Background: Quality of Life (QoL) in patients with colorectal cancer and liver metastases treated with selective internal radiotherapy (SIRT) using Yttrium-90 microspheres combined with FOLFIRI (standard chemotherapy) has not been compared to FOLFOX alone. We report QoL results from a prospectively pooled analysis of 9 multi-centre randomized trials: FOXFIRE, FOXXFIRE-Global and SIRFLOX.

Methods: Patients were randomized to FOLFOX or FOLFOX+SIRT in 14 countries. Second-line therapy was permitted upon disease progression. EORTC-QLQ-C30 and EuroQol. EQ-SD (3 level) questionnaires were given to all patients at baseline, 2, 6, 12 and 14 months from starting treatment and yearly thereafter, and at disease progression. We compared QoL scores between arms at each timepoint, calculating mean differences adjusted for baseline scores, using a 5% significance level. No missing data imputation was performed.

Results: 1103 patients were randomised overall. Questionnaire response rates ranged from 92% (1010/1092) at baseline to 35% (163/493) at 24 months. Patients randomised to SIRT showed significantly (p < 0.05) worse scores on 3 of 6 QLQ-C30 functioning scales and 3 of 9 symptom scales (fatigue, nausea and vomiting, appetite loss) at 4-8 weeks after treatment (2-3 months from baseline). SIRT patients had significantly better functioning scores on 3 of 6 scales at disease progression, and significantly less dyspnoea or constipation. Almost no other QLQ-C30 scales showed significant differences at 6, 12 or 24 months. The EQ-SD showed a statistically significant decrement of 0.02 in patients in the SIRT group 2-5 months from baseline, but no differences at other timepoints.

Conclusions: This analysis has shown that QoL is slightly impaired in functioning and symptom domains 4-8 weeks after treatment with SIRT+FOLFOX compared with FOLFOX alone, but slightly better when measured at disease progression. These differences were consistent between the QLQ-C30 and EQ-SD instruments. The differences detected were not large enough to be considered clinically significant.

Clinical trial identification: FOXFIRE ESDCTRIS6867199; SIRFLOX NCT00934503; FOXXFIRE-Global NCT012179954

Legal entity responsible for the study: University of Oxford

Funding: Bobby Moore Fund of Cancer Research UK; SirteX Medical Ltd

Disclosure: I. Chau: Advisory Board: Sanofi Oncology, Eli Lilly, Bristol-Myers Squibb, MSD, Bayer, Roche, Five Prime Therapeutics. Research funding: Janeway, Janssen, Sanofi Oncology, Merck Serono, Novartis. Honorarium: Taiho, Pfizer, Amgen, Eli Lilly, Gilead Science. S. Love: Grants from: Cancer Research UK, SirteX Medical and non-financial support from SirteX Medical. J. Mischandreas: Grants from Cancer Research UK, SirteX Medical and non-financial support from SirteX Medical. P. Videc: Grants from Cancer Research UK, SirteX Medical and non-financial support from SirteX Medical. P. Tait: Medical advisor and medical praction for SirteX medical. H. Wason: Grants, personal fees, non-financial support and other uncompensated work from SirteX Medical. G. Van Hazel: Compensation for participation in advisory committees from SirteX. P. Gibbo: Personal fees from SirteX. R. Sharma: Research funding, honoraria and consultancy fees from SirteX Medical. All other authors have declared no conflicts of interest.

Quality of life (QoL) analyses in patients with RAS wild-type (wt) metastatic colorectal cancer (mCRC) treated with first-line FOFOX-4 ± cetuximab in the phase 3 TAILOR trial


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Background: In the phase 3 TAILOR trial, adding cetuximab to first-line FOFOX-4 significantly improved progression-free survival (PFS), overall survival (OS), and overall response rate (ORR) in patients with RAS wt mCRC. Here we present QoL analyses.

Methods: TAILOR is a randomized phase 3 trial that includes a modified intention-to-treat population of 393 patients from China with RAS wt mCRC treated with FOFOX-4 ± cetuximab. The primary endpoint of TAILOR is PFS based on independent review; secondary endpoints include OS, ORR, and QoL. QoL is investigated using the European Organisation for Research and Treatment of Cancer Qol questionnaire core-30 (EORTC QLQ-C30). QoL assessments were planned to be performed at baseline, every 8 weeks of treatment thereafter, and at the final tumour assessment. Patients with RAS wt tumors are considered evaluable for QoL if they provide ≥ 1 evaluable EORTC QLQ-C30 from screening to end of evaluation. Pattern-mixture modeling is used to compare QoL between treatment groups by taking into account dropout pattern and other covariates.

Results: Among 393 patients with RAS wt tumors, 390 were evaluable for QoL. Before adjustment for several factors (treatment, time, dropout pattern, age, sex, ECOG performance status, number of disease sites, liver-only metastases, and interaction between treatment and dropout pattern), global health status/QoL showed slightly more deterioration in the FOFOX-4 + cetuximab arm vs FOFOX-4 arm; however, when these factors were included in the analysis model, the difference between treatment groups was not considered clinically relevant. Similar findings were obtained upon analogous evaluation of social functioning, an individual QoL-related dimension of interest in mCRC.

Conclusions: Adding cetuximab to first-line FOFOX-4 significantly improved PFS, OS, and ORR without negatively impacting QoL in TAILOR study patients with RAS wt mCRC, consistent with observations from earlier cetuximab pivotal trials. These observations confirm cetuximab in combination with FOFOX-4 as a standard-of-care first-line treatment regimen for patients with RAS wt mCRC.

Clinical trial identification: NCT01287384

Legal entity responsible for the study: Merck KGaA, Darmstadt, Germany

Funding: Merck KGaA, Darmstadt, Germany


Implementation, participation and satisfaction rates of a web-based decision support tool for patients with metastatic colorectal cancer

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Background: The use of decision support tools facilitates shared decision-making, but effective implementation of these tools with adequate patient and provider participation is challenging. Our study aims to effectively implement a newly developed patient-centred decision support tool for patients with metastatic colorectal cancer with sufficient patients’ and providers’ participation and satisfaction.

Methods: We conducted a patients’ and oncologists’ needs assessment and developed a decision support tool consisting of a consultation tool and web-based information about treatment options. Between July 2016 (launch) and February 2017, we measured patient participation with log in rates and time spent by online tracking and calculated participation summary scores (low, intermediate and high). Patient satisfaction was voluntarily obtained during online support. We measured oncologist participation in 11 centers by the number of oncologists that handed out at least 1 consultation tool. Satisfaction was measured by structured interviews and a survey.

Results: Implementation rates differed between 3 and 72 handed out (median 23) consultation tools per centre with a median patients’ log in rate of 57% (range 39-85%). The majority of patients (68%) had an intermediate high or high participation summary score. The median time spent during consultation was highest for questions about patients’ respective (5 mins) and colorectal cancer information (4 mins). Patient satisfaction was 76%. Oncologists’ participation per centre ranged from 25 to 100%. The average rating of the decision support tool was 7.8 (scale 1 to 10) by participating patients.
The current interim analysis indicates that aflibercept safety signals were identified from the current interim analysis. Pretreated with anti-EGFR antibody and/or bevacizumab, who showed a disease control rate of 73% in second line aflibercept therapy. This study is supported by Sanofi-Aventis Deutschland GmbH.

Quality-of-life in patients with metastatic colorectal cancer (mCRC) treated with aflibercept and FOLFIRI – interim results of the non-interventional AIO study QoLTrap

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Background: The anti-angiogenic fusion protein Afiblercept targets VEGF-A, VEGF-B and PIGF. Afiblercept in combination with FOLFIRI is approved in patients with mCRC that is resistant or has progressed after oxoptin-containing therapy.

Methods: QoL Trap (AIO-LQ-0113) is an international (Austria, Germany, Switzerland) non-interventional study with a recruitment target of 1500 patients. Primary goal is to evaluate Quality-of-life (QoL) in mCRC patients treated with aflibercept + FOLFIRI using the EORTC-QLQ-C30 questionnaire at baseline and at every cycle. Results: For this interim analysis (data cut-off: 02 March 2017) 576 patients (mean age: 64.7 ± 10 years; 65.1% male, 50.3% with documented RAS mutation, ECOG 0-1: 85.6% of patients) who completed the baseline and at least 2 post-baseline EORTC-QLQ-C30 questionnaires were evaluated. Afiblercept was administered for a median number of 6 (and up to 35) cycles. Patients had a median global health score of 58.3 which decreased for patients with no significant worsening in gastrointestinal, dyspnea, and sleep disturbance scales. 202 patients receiving study therapy as 2nd line treatment were treated with aflibercept + FOLFIRI using the EORTC-QLQ-C30 questionnaire at baseline and every cycle.

Conclusions: The current interim analysis indicates that aflibercept + FOLFIRI in mCRC patients under routine conditions was accompanied by a moderate decline in global health status. Preliminary efficacy results are encouraging, also for patients pretreated with anti-EGFR antibody and/or bevacizumab, who showed a disease control rate of 73% in second line aflibercept therapy. This study is supported by Sanofi-Aventis Deutschland GmbH.

Real world use of palliative systemic therapy (tx) in patients (pts) with metastatic early onset colorectal cancer (mEOCRC) within a UK specialist cancer centre

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Background: The incidence of EOCRC, defined as CRC diagnosed in pts 50 years old, is increasing. Current literature relating to the palliative systemic tx used, its efficacy, tolerability and outcomes in this group is sparse.

Methods: Retrospective analysis of pts with mEOCRC treated with systemic tx at the Royal Marsden Hospital (RMLH) between Jan 2009 – Dec 2014 was conducted. Results: 114 pts had palliative systemic tx. 93 had mEOCRC at diagnosis of whom 51% were male, median age 43 (range 21-49), 90% performance status ≤1. 72% had left (L) sided tumours. 4% had sigmoid cells. 2 pts had known hereditary syndromes. 72% had

<p>| Table: 597P |</p>
<table>
<thead>
<tr>
<th>Metastatic tx line</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>114</td>
<td>78</td>
<td>40</td>
<td>15</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>6.9</td>
<td>5.0</td>
<td>2.0</td>
<td>3.9</td>
</tr>
<tr>
<td>Best Response (HR)</td>
<td>CR 4 PR 40 SD 32 PD 32 NA 1</td>
<td>CR 1 PR 17 SD 26 PD 51 NA 5</td>
<td>PR 8 SD 23 PD 69</td>
<td>PR 7 SD 13 PD 73 NA 7</td>
</tr>
<tr>
<td>mOS from diagnosis if last line of tx, months</td>
<td>90</td>
<td>14.9</td>
<td>18.7</td>
<td>31.7</td>
</tr>
</tbody>
</table>

Chemotherapy-induced thrombocytopenia (CIT) in metastatic colorectal cancer (mCRC) patients

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Background: Thrombocytopenia is a common hematologic toxicity of myelosuppressive chemotherapy and can complicate a patient’s care.

Methods: This is a descriptive secondary analysis of data from two large clinical trials of mCRC patients - 1,178 treatment-naïve patients receiving fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) and 1,067 previously-treated patients receiving fluorouracil, leucovorin, and irinotecan (FOLFIRI) - to investigate the frequency and clinical consequences of CIT. Evidence of CIT was studied in two ways: 1) recorded platelet counts throughout the study (overall and by grade: <100-75x10⁹/L; [grade 1]; <75-50 [grade 2]; <50-25 [grade 3]; <25 [grade 4]); and 2) the occurrence of “thrombocytoenia” as an adverse event that directly resulted in platelet transfusion, chemotherapy discontinuation, and/or chemotherapy dose change/delay. The number, duration, and timing (with respect to chemotherapy cycle) of CIT episodes and the co-occurrence of neutropenia and/or anemia (overall and by grade), were also analyzed but not reported in this abstract.

Results: Evidence of CIT based solely on platelet count was relatively common in the FOLFOX4 study (37% of patients had ≥1 platelet count <100x10⁹/L) and less frequent in the FOLFIRI study (4%), during a median follow-up of approximately one year in each study. Evidence of grades 2, 3 and 4 thrombocytopenia were observed in 15%, 2%, and 1% of FOLFOX4 patients, respectively, and in 1%, <1%, and 0%, of FOLFIRI patients, respectively. Thrombocytopenia as an adverse event resulting in one of the clinical outcomes of interest occurred a total of 434 times across the two studies (FOLFOX4: 406; FOLFIRI: 27). Most events (97%) were addressed solely through a chemotherapy dose change and/or delay, but there were 4 events that were managed exclusively by chemotherapy discontinuation and 10 instances when a platelet transfusion was required (2 of which also led to chemotherapy discontinuation).

Conclusions: In mCRC patients receiving chemotherapy, thrombocytopenia can pose a real clinical problem, commonly leading to chemotherapy delays and/or dose reductions and in some cases, necessitating platelet transfusion and cessation of chemotherapy treatment.

Clinical trial identification: This was a secondary analysis of data from two clinical trials: NCT00364013 and NCT00339183

Legal entity responsible for the study: Amgen Inc


Legal entity responsible for the study: Sanofi Aventis GmbH

Funding: Sanofi Aventis Deutschland GmbH

Clinical trial identification: AIO-LQ-0113

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Background: Programmed cell death 1 (PD-1) and its ligand (PD-L1) are key suppressors of the cytotoxic immune response. PD-L1 expression on tumor cells may be induced by the immune microenvironment, resulting in immune escape, and an adverse prognosis in many malignancies. In colorectal carcinoma the response to PD-1/PD-L1 inhibition is correlated with microsatellite instability. However, little is known about the clinicopathological, molecular, and prognostic characteristics of colorectal carcinoma with PD-L1 expression. In surgically resected colorectal adenocarcinoma, micrometastasis should be crucial for recurrence, and micrometastasis may be related to PD-L1 expression in colorectal adenocarcinoma. PD-L1 expression is independent prognostic factors of disease-free survival (progression analysis revealed that pathologic N stage and High PD-L1 expression was an independent prognostic factor of disease-free survival (progression analysis revealed that pathologic N stage and High PD-L1 expression was an independent prognostic factor of disease-free survival (progression analysis revealed that pathologic N stage and High PD-L1 expression was an independent prognostic factor of disease-free survival (progression analysis revealed that pathologic N stage and High PD-L1 expression was an independent prognostic factor of disease-free survival (progression analysis revealed that pathologic N stage and High PD-L1 expression was an independent prognostic factor of disease-free survival (progression analysis revealed that pathologic N stage and High PD-L1 expression was an independent prognostic factor of disease-free survival (progression analysis revealed that pathologic N stage and High PD-L1 expression was an independent prognostic factor of disease-free survival (progression analysis revealed that pathologic N stage and High PD-L1 expression was an independent prognostic factor of disease-free survival (progression analysis revealed that pathologic N stage and High PD-L1 expression was an independent prognostic factor of disease-free survival (progression analysis revealed that pathologic N stage and High PD-L1 expression was an independent prognostic factor of disease-free survival.

Staging UICC

<table>
<thead>
<tr>
<th>Tumor Location</th>
<th>Staging</th>
<th>RCC</th>
<th>LCC</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>626</td>
<td>918</td>
<td>1544</td>
<td>(20.2%)</td>
</tr>
<tr>
<td>II</td>
<td>1091</td>
<td>979</td>
<td>2070</td>
<td>(27.1%)</td>
</tr>
<tr>
<td>III</td>
<td>995</td>
<td>1016</td>
<td>2011</td>
<td>(26.4%)</td>
</tr>
<tr>
<td>IV</td>
<td>863</td>
<td>807</td>
<td>1670</td>
<td>(21.9%)</td>
</tr>
<tr>
<td>Total</td>
<td>3739</td>
<td>3887</td>
<td>7626</td>
<td>(100.0%)</td>
</tr>
</tbody>
</table>

Results: Tumor location per se in stage III and IV colorectal cancer in the current retrospective, epidemiological study, revealed a significantly better overall survival for LCC than for RCC in stage III and IV in a univariate analysis. After stratification by age, hazard ratio was 0.91 (95% confidence interval 0.79-1.07) in stage III and 0.79 (95% confidence interval 0.66-0.84) in stage IV, thereby confirming recent, retrospective data from large phase III clinical trials (FIRE-3, CRISTAL, PEAK and PRIME).

Conclusions: Real life registry data of a well-defined colorectal cancer population confirm retrospective clinical trial data that LCC in stage III and IV carry a more favourable outcome than RCC, even in the era of modern chemo-immunotherapy.

Legal entity responsible for the study: Alois H. Lang

Funding: Krebsregister Vorarlberg

Disclosure: All authors have declared no conflicts of interest.

Real life registry data of primary localisation of a well-defined colorectal cancer population of western Austria (Salzburg, Tyrol and Vorarlberg), eastern Switzerland (St. Gallen and Graubünden) and Liechtenstein

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Background: Clinical guidelines are designed to prevent undesired practice variation where high quality evidence or expert consensus is available. However, reading and interpretation of test-based guidelines is time-consuming and might be difficult to apply in routine daily practice. Therefore, the aim of our study is to examine the feasibility of converting the Dutch multidisciplinary colorectal cancer guideline recommendations into data driven algorithms (decision trees) to facilitate guideline usage.

Methods: We converted the most recent Dutch colorectal cancer guideline (published in 2014) into decision trees modelled by decision nodes representing patient or disease characteristics ultimately branching into guideline recommendations. Where no evidence-based, decision trees were discussed with an expert panel until agreement was reached. Thereafter, the developed decision trees were published in open access decision support software.

Results: In total, we developed 34 decision trees driven by 101 decision nodes. Decision trees focused on recommendations for diagnostics (n = 1) staging (n = 10), treatment (colon: n = 1, rectum: n = 5; both: n = 9), pathology (n = 4), follow-up (n = 3) and overview decision tree. We identified guideline recommendation information gaps for example specific surgical policy related to (the number of) lung metastases, a recommendation about follow-up schemes after resection or local treatment (e.g. RFA) of metastases and the period between neo-adjuvant treatment and re-staging. It was...
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Background: Colorectal cancer (CRC) incidence is declining rapidly overall in most European countries. Curiously, in the United States, a worrisome increase in incidence has recently been reported among young adults. We report the first study on this specific age group in the European population.

Methods: This retrospective study was conducted in Crete, Greece using data on malignant neoplasms of the colon (ICD-10: C18), rectosigmoid junction and rectum (ICD-10: C19-20). Data were obtained from the database of the regional Cancer Registry of Crete (1) and coded according to the international classification system for Oncology (ICD-O-2). Information on patient's demographic profile, personal and family medical history, and lifestyle factors (smoking habits, alcohol consumption) were also available.

Results: The mean age-specific incidence rates (ASIR) of CRC patients < 50 years at diagnosis were 5.1/100,000/year, while for patients > 50 years the ASIR was 150/100,000/year. The rates were significantly higher for male patients compared to females (p < 0.02), especially between the ages of 30 and 70 years. Contrary to that, females aged 20-24 years presented slightly higher ASIR comparing to males. Focusing on patients < 50 years, significant percentage changes of incidence rates per year (p < 0.05) are observed for both colon and rectal cancer. The age group of 20-34 years presented a 29.7% increase from 1992 to 2013, while the increase for the period 2014 to 2024 is expected to reach 36.9%. Similar increases were observed in the age group of 35-49 years.

Conclusion: The increase in colorectal cancer occurrence among young adults with CRC is high, efforts to promote research and awareness among patients and physicians about the unique characteristics of early-onset CRC are critical.

Legal entity responsible for the study: Greek Society of Oncology

Disclosure: All authors have declared no conflicts of interest.

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Epidermoid colorectal cancer in Korea: Korean National Health Insurance bigdata analysis

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Background: This study was conducted to demonstrate the epidemiology of colorectal cancer (CRC) in Korea using the by analysis of big data using the Korean National Health Insurance Service (NHIS).

Methods: We analyzed the NHIS database of patients admitted hospitals which received its quality assessment of CRC between 2011 and 2014.

Results: We included 71,513 colorectal cancer patients. Median follow-up duration was 3.2 years (range 0.003-5.5 years). Male patients were 60.1% and median age was 65 years old (interquartile range 56-73). The stage at diagnosis was stage I in 22.0%, stage II 29.9%, stage III 35.6%, stage IV 12.9%. As primary site according to surgery code, colon is 61.7% and rectum is 38.3%. Patients with adenocarcinoma were 96.5%. Survival probability at 5 year elderly patients (>70 years old) showed worse survival rate than that of patient with age <70 [HR 2.24, 95% confidence interval (CI) 2.17-2.32]. By stage, survival probability at 5 year is 91.9% with stage I, 82.8% with stage II, 73.8% with stage III, and 30.4% with stage IV.

Conclusion: These results show epidemiology and survival of CRC in Korea. Our study was the first to describe these data for colorectal cancer at a nationwide level.

Legal entity responsible for the study: Sun Kyung Baek

Funding: None

Disclosure: All authors have declared no conflicts of interest.

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Watch and wait versus surgery with pathological complete response: Single institution experience

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Background: Neoadjuvant chemoradiotherapy improves local control, may lead to significant tumor regression and even complete pathological response. We compared patients managed by watch and wait approach and those submitted to surgery with pathological complete response.

Methods: We included patients with rectal adenocarcinoma who had received neoadjuvant long-course chemoradiotherapy (45-50.4 Gy in 25-28 daily fractions with concurrent fluoropyrimidine-based chemotherapy) between July 2003 and December 2012. After, we compared outcomes between two groups: 1) 39 patients managed with watch and wait (WW) approach after clinical complete response; 2) 68 patients submitted to surgery and had pathological complete response (pCR). The primary endpoint was relapse-free survival (RFS).

Results: The median age was 63.5 years of age (45-81) for WW and 60 (29-86) for pCR. After median follow up of 73 months, 39 (45.4%) patients managed by watch and wait were alive and 8 (11.8%) patients had local relapse, while 3 (4.4%) patients had both. Survival surgery was possible in 5 (62.5%) patients after local relapse and 1 (3%) patient after local and distant relapse in WW group, but was not possible in any patient in pCR group.

Conclusion: The watch and wait approach had worse RFS than WW surgery in patients with metastatic colorectal cancer. Radical rectal surgery was avoided in 62.5% of patients selected and salvage surgery was possible in 62.5% of patients who had local relapse in WW group. The odds of permanent colostomy were 2.6 higher in pCR group.

Legal entity responsible for the study: INCA - Instituto Nacional de Cancer

Funding: None

Disclosure: All authors have declared no conflicts of interest.

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A retrospective cohort study evaluating the safety and efficacy of TAS-102 in patients with metastatic colorectal cancer (HGC5G1503): Updated analysis

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Background: TAS-102 was approved in Japan, however, there are few studies exploring the efficacy and safety of TAS-102. The J003 trial and RECOURSE trial revealed the safety and efficacy of TAS-102 was approved in Japan, however, there are few studies exploring the efficacy and safety of TAS-102.

Methods: We analyzed the NHIS database of patients admitted hospitals which received its quality assessment of CRC between 2011 and 2014.

Results: We included 71,513 colorectal cancer patients. Median follow-up duration was 3.2 years (range 0.003-5.5 years). Male patients were 60.1% and median age was 65 years old (interquartile range 56-73). The stage at diagnosis was stage I in 22.0%, stage II 29.9%, stage III 35.6%, stage IV 12.9%. As primary site according to surgery code, colon is 61.7% and rectum is 38.3%. Patients with adenocarcinoma were 96.5%. Survival probability at 5 year elderly patients (>70 years old) showed worse survival rate than that of patient with age <70 [HR 2.24, 95% confidence interval (CI) 2.17-2.32]. By stage, survival probability at 5 year is 91.9% with stage I, 82.8% with stage II, 73.8% with stage III, and 30.4% with stage IV.

Conclusion: These results show epidemiology and survival of CRC in Korea. Our study was the first to describe these data for colorectal cancer at a nationwide level.

Legal entity responsible for the study: Sun Kyung Baek

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Annals of Oncology

Methods: We retrospectively analyzed the clinical data of 411 patients who received TAS-102 in the multi-institutional retrospective study (HGCSG1503). This study was analyzed by CTCAE v4.0 for adverse events (AEs), RECIST v1.1 for response rate (RR)/disease control rate (DCR), and Kaplan-Meier method for progression-free survival (PFS) and overall survival (OS).

Results: Patients characteristics were as follows: male/female 218/193, median age 66 (range 33-88), ECOG PS 0 (10/22) 170/190/43/8, KRAS Exon2 wild/mutant 210/187 (14 patients; KRAS Exon2 was not tested). The initial starting dose was 70 mg/m² (n = 326, 79.3%) and reduced dose (n= 85, 20.7%). Dose reductions were required in 101 patients (24.6%). The common grade 3 AEs were neutropenia count decreased (48.1%), white blood cell decreased (34.8%), and anemia (28.7%). RR and DCR were 0.35% and 37.2%, respectively. Median PFS and OS were 2.2 and 7.3 months. In analysis on the relationship between ECOG PS 0-1 and PS 2-3, DCR was 38.7% vs. 26.7% (p = 0.140), median PFS was 2.3 vs. 1.5 months (HR 2.000, p < 0.001), and MFS was 8.1 vs. 3.4 months (HR 2.278, p < 0.001).

Conclusions: In this analysis, TAS-102 in the real-world clinical practice showed slightly higher anemia to the previous pivotal clinical trials. Although the efficacy in patients with PS 0-1 was similar to the previous reports, TAS-102 did not show the effi- cacy for patients with PS 2-3.

Clinical trial identification: UMIN000020551, 2016/02/02

Legal entity responsible for the study: Non-profit organization: Hokkaido Gastrointestinal Cancer Study Group

Funding: Non-profit organization: Hokkaido Gastrointestinal Cancer Study Group


605P Preliminary results on germline and somatic molecular investigations in Romanian Lynch syndrome patients

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Background: Up to 30% of colorectal cancers (CRCs) have evidence of a familial component, and about 5% are thought to be due to inherited mutations in MMR (Mismatch Repair) genes. Lynch syndrome (LS) is characterized by a very early onset and lifetime risk estimated to 80%. The gold standard for LS diagnosis is complete Sanger sequencing, a very complex and expensive analysis. MMR mutations are de- tected in only 60% of criteria fulfilling families, while they are present in up to 20% of families not fulfilling these criteria and which are implicitly excluded from genetic counselling. Therefore, we propose an alternate algorithm, based on germline and tumor analysis, intended to increase molecular diagnostic efficiency and CRC causality coverage.

Methods: 20 LS families were selected according to Amsterdam criteria, and one index case per family agreed to participate by signing informed consent. All coding regions of MMR (MLH1, MSH2, MSH6, PMS2, and MSH4) were screened by direct sequencing. All variants were interpreted by in-silico analysis. MLPA was performed for large genomic rearrangements. MMR protein expression in tumors was investigated by immunohistochemistry. Somatic tumor DNA was checked for microsatellite instability (MSI), MLH1 promoter hypermethylation (PHM), as well as for somatic BRAF V500E mutation.

Results: Over 50% of our samples presented germline variants, the majority being benign. Four unclassified variants are altering splicing enhancers. One deleterious variant, as for BRAF V600E mutation.

Conclusions: In our preliminary study, we have identified a number of deletions and rearrangements in MMR genes, which can help elucidate the molecular basis of Lynch syndrome. Further research is needed to confirm these findings and to determine their clinical implications.

605P Clinical manifestations and prognostic factors of bone metastasis in colorectal cancer


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Background: Bone metastasis from colorectal cancer (CRC) is known as a poor prognostic factor. However, the clinical manifestations and outcomes of CRC with bone metastasis are uncertain.

Methods: CRC with bone metastases were searched from January 2006 to April 2016, and bone metastasis was diagnosed by plain x-ray, computed tomography (CT), magnetic resonance image (MRI), whole body bone scan (WBBS) or positron emission tomography (PET). Clinical data including site of bone metastasis, visceral metastasis, laboratory finding at diagnosis of bone metastasis, and KRAS mutation were reviewed.

Results: Of 12,005 CRC patients, 321 (2.7%) had bone metastasis. Colon cancer (58.5%) is more than rectal cancer (41.5%), and pattern of metachronous bone metastasis was 66% (1.7%). Median time to bone metastasis was 28.2 months from diagnosis of CRC in metastatic patients. The most common bone metastasis site was spine (69.5%) and followed by pelvic (51.2%) and long bone (21.6%). At the time of bone metastasis, liver (57.8%), lung (31.7%) peritoneal (23.8%) metastasis was also observed, and bone only metastases was 28 (8.5%) patients. High neutrophil, high LYMPH, low ALB, low CRP, low MCH, high ALP, high ALB, high HbA1c, low CD4 count (NLR, ≥ 3.0), allisphage factor (APC), low TGF beta, high interleukin-6, low MCHC, high Vilsken index, high tumor necrosis factor (TNF), high ferritin, low fibrinogen, low albumin, low C-reactive protein (CRP), high tumor protein p53, low folate, high ESR, high PLT, and low FPG were independent factors for OS. Bone only metastases is the most significant prognostic factor for bone metastasis of CRC.

Conclusions: Bone metastasis of CRC is not a rare event and has a poor prognosis. Bone only metastases is the most significant prognostic factor and further studies are needed.

Legal entity responsible for the study: Yonsei Cancer Center, Yonsei University Health System

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Background: A recent American Cancer Society study showed that the rate of colorectal cancer (CRC) in young American adults is rising. There are limited data on young Arabian adults with CRC. Herein we explore differences between American and Egyptian young adults with CRC.

Methods: A retrospective review of young (<46 years old) patients (pts) with CRC in the United States (US-pts) and Egypt (EGY-pts) was undertaken. T and Fisher's exact tests were used for comparative analyses. Kaplan-Meier methodology estimated survival.

Results: In total, 504 pts with CRC were studied, incorporating 62 US-pts (median age 38 yrs, range 20-46) and 442 EGY-pts (35 yrs, 15-46). US-pts were commonly more female (66% vs 41%, p < 0.001) and had more colon primaries (75% vs 50%, p = 0.011). EGY-pts had more left-sided tumors (78% vs 61%, p = 0.008), of which 49% were rectal primaries (vs 24% for US-pts, p < 0.001). US-pts had more well-differentiated tumors (23% vs 3%, p < 0.001), whereas EGY-pts had more mucin-producing tumors (40% vs 26%, p = 0.042). US-pts were more likely to have bowel obstruction (64% vs 17%, p < 0.001) and present with metastatic (met) disease (66% vs 28%, p < 0.001), particularly in the liver, lung, and peritoneum (56% vs 40%, p = 0.04, 35% vs 9%, p < 0.001; 48% vs 16%, p < 0.001). Comparing US-pts with met disease, EGY-pts tended to have rectal primaries (33% vs 22%), whereas US-pts had more right-sided tumors (38% vs 19%, p = 0.03). US-pts were more likely to undergo palliative resection or metastectomy (41% vs 26%, p = 0.039) and receive bevacizumab (69% vs 16%, p < 0.001). EGY-pts received more 5-FU alone (39% vs 2%, p < 0.001) or 5-FU + radiation (40% vs 0%, p < 0.001), whereas US-pts received more FOLFOX/FOLFIRI (64% vs 13%, p < 0.001). There was no statistically significant difference in median overall survival between US-pts (Not Reached) and EGY-pts (76 months, mos) vs (6.6), nor median progression free survival between US-pts (20 mos) and EGY-pts (13 mos, p = 0.202).

Conclusions: Significant differences were observed among young US-pts and EGY-pts with CRC, particularly primary tumor location, patterns of metastasis, and treatment used. Further evaluation of the environmental and ethnic impact on disease biology and treatment outcomes is warranted.

Legal entity responsible for the study: Georgetown University IRB

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Nivolumab, ipilimumab and COX2-inhibition in early stage colon cancer

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Background: For the 4% of patients with metastatic mismatch repair deficient colon cancers, effective therapy is still an unmet need. In the past years COX2 inhibitors have been shown to improve responses to anti-PD1 therapy in patients with MSS colorectal cancer. For these reasons a phase II trial is designed to investigate the safety and feasibility of preoperative immunotherapy in CCs. The primary objective will be to determine the safety and feasibility of preoperative immunotherapy in CCs. Secondary objectives include exploring the immune activating capacity of immunotherapy in early stage CCs and the added effects of COX2 inhibition, changes in immune suppressive pathways and the correlation of mutational load to putative markers of response. After additional tumor biopsies are taken via endoscopy, patients with mCRC patients will be treated with a single dose of ipilimumab 3mg/kg on day 1 and two cycles of nivolumab 1mg/kg on day 1 and 15. Patients with MSI tumors will be randomized to receive celecoxib 200mg once daily in combination with abovenamedin treatment. After 5-6 weeks, patients will undergo surgery, where tumor and normal tissue will again be harvested. When deemed advisable by the pathologist report, standard adjuvant treatment with chemotherapy will be offered. A total of 30 patients with MSS tumors and 30 patients with MSI tumors will be enrolled. Recruitments for this study are ongoing and currently two patients have been enrolled.

Conclusion: This is, to our knowledge, the first study exploring pre-operative immunotherapy in patients with MSI colorectal cancer and will hopefully help to identify mechanisms that interfere with clinical activity of immunotherapy, and to develop future strategies and combinations for CRC.

Clinical trial identification: 2016-002940-17. Release date: January 2017

Legal entity responsible for the study: Netherlands Cancer Institute

Funding: Bristol-Myers Squibb

Disclosure: D. Cullen: Employment with BMS. J.B. Haanen: Ad board BMS. All other authors have declared no conflicts of interest.

TRIUMPH Study: A multicenter Phase II study to evaluate efficacy and safety of combination therapy with trastuzumab and pertuzumab in patients with HER2-positive metastatic colorectal cancer (EPOC1602)


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Background: HER2 amplification is identified in approximately 5% out of RAS wild-type metastatic colorectal cancer (mCRC) and likely related to the resistance to EGFR blockade. Some preclinical and clinical studies have shown the efficacy of HER2-targeted therapy against HER2-positive mCRC. To identify this orphan fractionated mCRC, we collaborate with the nationwide genome cancer screening project (SCRUNJapan GI-Screen) by means of tissue/circulating tumor DNA (ctDNA) screening. The primary objective will be to determine the safety and feasibility of preoperative combination therapy with trastuzumab and pertuzumab in patients with HER2-positive mCRC confirmed by either tissue or ctDNA analysis. Eligibility criteria includes historically confirmed mCRC, EGFR PS ≤ 2, RAS wild-type and HER2-positive defined as HER2 Ki > 2.0 (HER2/C20 ratio > 2.0) by means of tissue screening, or HER2-amplified and RAS wild-type identified from ctDNA (Guardant360); and refractory or intolerant to fluoropyrimidine, irinotecan, oxaliplatin, and anti-EGFR antibody. Enrolled patients will receive intravenous trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg) and pertuzumab (840 mg loading dose, followed by 420 mg) every 3 weeks. In addition, the natural history data of patients with HER2-positive and RAS wild-type who do not meet the eligibility will be followed as a historical control. The primary endpoint is objective response rate (ORR) by investigator’s assessment in patients with HER2 positive tumor confirmed by tissue analysis as well as ctDNA analysis, respectively. A sample size for each group is calculated to be 18 on the basis of a power of 80% to test the null hypothesis of ORR of less than 5% versus the alternative hypothesis of ORR of over 30%, at a one-sided alpha level of 0.025. Furthermore, ctDNA will be serially analyzed to investigate the resistance mechanisms; a key focus of current research is to provide clinically meaningful thresholds which may be used for identifying and implementing treatment changes.

Legal entity responsible for the study: Wataru Okamoto

Funding: The Japan Agency for Medical Research and Development

Background: Developing appropriate therapy for colorectal cancer is one of the most important health issues worldwide. The CORRECT study was a Phase III, international, placebo-controlled study in which the case data was accumulated from 17 countries including Japan. The results showed the overall survival (OS), the primary endpoint, was significantly prolonged in the regorafenib group, compared with the placebo group. A total of 760 patients were enrolled in the CORRECT study, including 100 Japanese patients. On the other hand, the administration method of regorafenib does not depend on the height, weight, or race of the patients, or other parameters, and 160 mg/body/day is the standard starting dose. The study was performed (in the patients with metastatic colorectal cancer considered as unresectable due to distant metastasis or locally advanced cancer, indicating disease progression during the standard chemotherapy or within three months after the last administration of the standard chemotherapy, with adequate bone marrow reserve and organ function. The standard chemotherapy includes fluoropyrimidine, oxaliplatin, irinotecan, and bevacizumab, and anti-EGFR (in case of patients with only RAS WT). Treatment history of TAS-102 is not allowed. Regorafenib 120 mg/body/day is orally administered once a day, after meal for 3 weeks (Days 1 to 21), followed by a 1-week treatment-off period (Days 22 to 28). This 4-week period is considered as 1 cycle and shall be repeated until progression of disease based on RECIST v1.1. The purpose of the study is to evaluate the efficacy and safety of regorafenib when regorafenib treatment at 120 mg/day for the patients with metastatic colorectal cancer.

Primary endpoint: disease control rate (> = 6 weeks). Secondary endpoints: OS, progression-free survival, response rate, safety, and drug adherence.

Legal entity responsible for the study: Toshihiro Kudo

Funding: Bayer Yakuhin, Ltd., Japan.

Disclosure: T. Kudo: I belong to a donated fund laboratory from Yakult Honsha Co., Ltd., Chugai Pharmaceutical Co., Ltd., and Ono Pharmaceutical Co., Ltd. T. Satoh: Honoraria and consulting fee from: Eli Lilly, Chugai, Merck Serono. Research funding (to institution) from: Sanofi, Yakult Honsha, Chugai, Ono. All authors have declared no conflicts of interest.

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A Phase 3 Study of nivolumab (Nivo) in previously treated advanced gastric or gastroesophageal junction cancer (G/GEJ) cancer: Updated results and subset analysis by PD-L1 expression (ATTRACTION-02)


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Background: Nivo monotherapy demonstrated its efficacy with manageable safety for G/GEJ cancer refractory or intolerant to standard chemotherapy at the primary analysis (ATTRACTION-02) [ONO-4358-12]: ASCO GI 2017, Kang YK et al. J Clin Oncol. 2017; 35 (suppl 4S abstract 2). Here, we report updated results, and the relationship between efficacy of Nivo and PD-L1 expression levels.

Methods: 493 patients (pts) aged ≥ 20 years with ECOG PS 0-1 and unacceptable advanced or recurrent G/GEJ cancer after failure of two or more previous chemotherapy regimens were randomized in a 2:1 ratio to receive 3 mg/kg Nivo (N) or placebo (PLA). Pts were randomised 1:1 to PLA + H + CT (standard chemotherapy regimen) or P + H + CT. P and H were given every 3 weeks until disease progression or unacceptable toxicity (P at 840 mg, H: 8 mg/kg loading and 6 mg/kg maintenance doses). CT was given as per standard regimens/doses. Stratification factors were world region, prior gastrectomy and HER2 immunohistochemistry score. Primary endpoint was OS. Secondary endpoints included PFS and safety. JACOB was estimated to have 80% power to detect a significant improvement in OS (hazard ratio [HR] 0.777) at the final efficacy analysis after 502 events (overall two-sided 5% level).

Results: From 10 Jun 2013 to 12 Jan 2016, 388 pts were randomised to P + H + CT and 392 to PLA + H + CT. After a median OS follow-up of approx. 2 years, 504 patients had died, 242 in the P + H + CT arm (median OS 17.5 months) and 262 in the PLA + H + CT arm (median OS 14.2 months) (HR 0.84, 95% confidence interval [CI] 0.71–1.00; p = 0.0361). Median PFS was 8.5 months and 7 months respectively (HR 0.73, 95% CI 0.62–0.86). The safety profile was generally comparable between treatment arms except for diarrhoea (all grades: 61.6% in P + H + CT vs 35.1% in PLA + H + CT). Incidence of symptomatic and asymptomatic left ventricular systolic dysfunction was low and similar in both arms.

Conclusions: The study did not demonstrate a statistically significant improvement in OS with the addition of P to H + CT, although a 3.3-month increase in median OS was observed. P was generally well tolerated and no new safety signals were identified. Further analysis will be presented.

Clinical trial identification: Protocol number: R025114; ClinicalTrials.gov NCT01774786

Legal entity responsible for the study: Dr. H. Dillner, Uppsala University Hospital, Sweden

Funding: This study was supported by Ono Pharmaceutical Co., Ltd

Disclosure: The authors have no relevant conflicts of interest to declare.

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Legal entity responsible for the study: F. Hoffmann-La Roche Ltd

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Background: A recent phase 3, randomized, open-label, noninferiority trial compared the efficacy and safety of LEN to SOR as first-line systemic treatment in unresectable HCC (954 patients). The study included analyses to evaluate the impact of therapy for HCC on HRQOL.

Methods: HRQOL was assessed using the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire (EORTC QLQ-C30), the HCC-specific module (EORTC QLQ-HCC18), and the European Quality of Life (EQ-5D-3L) at baseline, Day 1 of each cycle, and off-treatment visit. Changes from baseline in both treatment arms were assessed using linear mixed models with selected covariates (baseline score, geographical region, macroscopic portal vein invasion and/or extrahepatic spread, ECOG-PS, body weight). Time to worsening for each domain was represented as months to deterioration defined by a minimally important difference (MID).

Results: A total of 954 patients (LEN treatment n = 478; SOR treatment n = 476) were randomized and included in the intent-to-treat population. Baseline HRQOL scores were similar for patients receiving LEN or SOR across all domains. Significant changes from baseline HRQOL scores were noted for Nutrition, Diarrhea, Role Function (RF), Pain, and Body Image (BI). In the QLQ-HCC18 Nutrition domain, lower adjusted mean scores in favor of LEN were reported at most points with significant differences at Cycle 6 and Cycle 9 (p < 0.05). SOR was associated with worsening Diarrhea symptoms with lower adjusted mean scores in favor of LEN reported at Cycles 3, 6, 9, and 12 (p < 0.01). Median months to clinically meaningful worsening among each treatment group was statistically significant favoring LEN for the QLQ-C30 domains of RF (2.0 vs 1.9; p = 0.0099), Pain (2.0 vs 1.8; p = 0.0060), and Diarrhea (4.6 vs 2.7; p < 0.0001), and in the QLQ-HCC18 domains of BI (2.8 vs 1.9; p = 0.0041), and Nutrition (4.1 vs 2.8; p = 0.0060).

Conclusions: Most domains met the noninferiority assumption between LEN and SOR. The additional evidence of significant HRQOL benefits further support LEN in terms of functional deterioration delays.

Clinical trial identification: NCT01761266

Legal entity responsible for the study: Eisai Inc

Funding: Eisai Inc


Results: From 60 sites in Japan, 386 patients were consented, and 195 patients were randomized (tivantinib; n = 134, placebo; n = 61). As results, median PFS was 2.8 months in the tivantinib group, whereas 2.3 months in the placebo group (HR = 0.72 [95% CI 0.51-1.02], p = 0.065). Median OS at the time of analysis was 9.9 months in the tivantinib group, whereas 8.5 months in the placebo group (HR = 0.85 [95% CI 0.59-1.22], but additional follow up may be needed to confirm long-term outcome. Grade 3 AE occurring ≥5% were neuropathy (31.6%), leukopenia (24.8%), lymphopenia (7.5%), anemia (14.3%) and febrile neutropenia (6.0%) in the tivantinib group, whereas none in the placebo group. New toxic profile was not identified except for known AE in the previous study.

Conclusions: Although favorable survival were observed in the tivantinib group, this study in Japan could not show the significant clinical benefit of tivantinib as a second-line therapy for hepatocellular carcinoma (HCC) with high expression of c-Met. A previous phase 2 study suggested a clinical benefit of tivantinib as a second-line therapy for hepatocellular carcinoma (HCC) with high expression of c-Met. This Japanese study aimed to confirm the efficacy and safety of tivantinib in this population (NCT01208157).

Methods: Main inclusion criteria were HCC patients refractory or intolerant to a prior sorafenib therapy, Child Pugh A, ECOG PS ≤1, at least one measurable lesion according to RECIST 1.1, and diagnosed as c-Met high [regarded as ≥2+ in ≥25% of tumor cells, by IHC]. Enrolled patients were blindly randomized to either tivantinib or placebo in 2:1 ratio. Stratification factors were vascular invasion (Y/N) and ECOG PS (0, 1). Tivantinib (120 mg bid) or placebo was orally administered until discontinuation criteria was met. Primary endpoint was PFS by the independent review committee, based on CT/MRI every 6 weeks. Secondary endpoints included OS and safety. A sample size of 160 patients and 136 PFS events were calculated to detect a HR of 0.6 (improvement in median PFS from 8 to 13.3 weeks), with 10% dropout, 80% power, and log-rank test with 5% two-sided alpha.

Results: From 60 sites in Japan, 386 patients were consented, and 195 patients were randomized (tivantinib; n = 134, placebo; n = 61). As results, median PFS was 2.8 months in the tivantinib group, whereas 2.3 months in the placebo group (HR = 0.72 [95% CI 0.51-1.02], p = 0.065). Median OS at the time of analysis was 9.9 months in the tivantinib group, whereas 8.5 months in the placebo group (HR = 0.85 [95% CI 0.59-1.22], but additional follow up may be needed to confirm long-term outcome. Grade 3 AE occurring ≥5% were neuropathy (31.6%), leukopenia (24.8%), lymphopenia (7.5%), anemia (14.3%) and febrile neutropenia (6.0%) in the tivantinib group, whereas none in the placebo group. New toxic profile was not identified except for known AE in the previous study.

Conclusions: Although favorable survival were observed in the tivantinib group, this study in Japan could not show the significant clinical benefit of tivantinib as a second-line therapy for c-Met high HCC.

Clinical trial identification: NCT02092157

Legal entity responsible for the study: Kyowa Hakko Kirin

Funding: Kyowa Hakko Kirin


Results: From 60 sites in Japan, 386 patients were consented, and 195 patients were randomized (tivantinib; n = 134, placebo; n = 61). As results, median PFS was 2.8 months in the tivantinib group, whereas 2.3 months in the placebo group (HR = 0.72 [95% CI 0.51-1.02], p = 0.065). Median OS at the time of analysis was 9.9 months in the tivantinib group, whereas 8.5 months in the placebo group (HR = 0.85 [95% CI 0.59-1.22], but additional follow up may be needed to confirm long-term outcome. Grade 3 AE occurring ≥5% were neuropathy (31.6%), leukopenia (24.8%), lymphopenia (7.5%), anemia (14.3%) and febrile neutropenia (6.0%) in the tivantinib group, whereas none in the placebo group. New toxic profile was not identified except for known AE in the previous study.

Conclusions: Although favorable survival were observed in the tivantinib group, this study in Japan could not show the significant clinical benefit of tivantinib as a second-line therapy for c-Met high HCC.

Clinical trial identification: NCT02092157

Legal entity responsible for the study: Kyowa Hakko Kirin

Funding: Kyowa Hakko Kirin

YOSEMITE: A 3 arm double-blind randomized phase 2 study of gemcitabine, paclitaxel-protein bound particles for injectable suspension, and placebo (GAP) versus gemcitabine, paclitaxel protein-bound particles for injectable suspension and either 1 or 2 truncated courses of demcizumab (GAD)

A. Cubillo Gracian,1 A. Dean,2 A. Muñoz,3 M. Hidalgo,4 R. Pazo-Cid,5 M. Martin,5 T. Macarulla Mercade,6 L. Lipriot,7 M. Harris,8 J.L. Marzano-Hlazo,9 J. Mauleón,10 C. Guillen-France,11 N. Tebbutti,12 P. Coaray,13 D. Schal,14 M. Zalupski,15 T. Kolevski,15 R. Stagg,16 D. Goldstein17


Background: Delta-like ligand 4 (DLL4) is a ligand that activates the Notch pathway which is important for cancer stem cell (CSC) survival. Demcizumab is a humanized, anti-DLL4 antibody that has been shown using an in vitro tumorigenicity limiting dilution assay to inhibit tumor growth and decrease CSC frequency in minimally passaged human xenograft models. In addition, inhibition of DLL4 has also been shown in preclinical studies to cause dysfunctional sprouting of new vessels resulting in an antiangiogenic effect. Encouraging data from a Phase 1b study of paclitaxel-protein-bound particles for injectable suspension (Abraxane), gemcitabine and demcizumab in patients with 1st line metastatic pancreatic cancer led to this double blind randomized 3 arm placebo-controlled Phase 2 study.

Methods: Patients with metastatic pancreatic cancer were randomized (1:1:1) to 1st-line therapy with either Arm 1 - GAP, Arm 2 - GAD with a single 70 day truncated course of demcizumab or Arm 3 - GAD with two 70 day truncated courses of demcizumab (second course starting on Day 168). GA were given at usual dose & schedule, P/D dose was given IV on days 1 and 15 in cycle 1-3 & 7-9. The primary endpoint was progression-free survival and secondary endpoints included response, survival, safety, immunogenicity, pharmacokinetics, and biomarkers of Notch signaling and CSC in blood, hair follicles and tumor cells. The primary study analyses compared GAP to the two pooled GAD arms.

Results: 207 patients were randomized and 204 were treated. The median age was 63, the male/female ratio was 116/88, the ECOG 0 vs 1 distribution was 98/106, the median # metastatic sites was 2 and 74% had hepatic metastases. The response/clinical benefit rates were 41.2%/70.6% vs 33.3%/74.3% in the GAP and pooled GAD arms, respectively. The median progression-free survival (PFS) (mPFS) was 5.5 months in the GAP and pooled GAD arms. The interim median overall survival (OS) for the GAP and pooled GAD arms were not reached and 13.2 months (HR = 1.02), respectively. Geographic differences in OS were observed. GAP was generally well tolerated with nausea, diarrhea, anemia, peripheral edema and fatigue being the most common reported toxicities. The incidence of the Grade 3 or greater toxicities of special interest with demcizumab therapy were hypertension (7.4% vs 16.2%), pulmonary hypertension (0% vs 0.7%), heart failure (0% vs. 3.7%), and bleeding (1.5% vs. 8.1%) in the GAP and pooled GAD arms, respectively. No cases of Grade 3 heart failure or pulmonary hypertension occurred during the 2nd 70 day course of demcizumab.

Conclusions: The addition of either 1 or 2 truncated courses of demcizumab to 1st line gemcitabine and Abraxane did not improve the efficacy compared to GAP in patients with 1st line metastatic pancreatic cancer. GAD therapy was generally well tolerated.

Clinical trial identification: NCT02289989 - November 10, 2014

Legal entity responsible for the study: OncoMed Pharmaceuticals

Disclosure: R. Stagg Employee and own stock of OncoMed. All other authors have declared no conflicts of interest.
Background: Treatment options for pts with LAPC are limited. In the phase 3 MPACT trial, nab-P + G treatment (Tx) resulted in a 3 + 3-fold reduction in primary pancreatic tumor burden vs G in pts with metastatic PC, suggesting that the regimen may be effective in LAPC. Interim efficacy and safety results from the international, multicenter, prospective phase 2 LAPACT trial are presented.

Methods: During induction, treatment-naïve pts with unresectable LAPC and ECOG 2 advanced PDAC were enrolled. Median age was 71/68 y, 51/55% were male and 91/83% had metastatic disease (liver 63/62%). Most frequent grade 3-4 toxicity per arm were anemia (12/7%), thrombocytopenia (7/11%), febrile neutropenia (3/4%), asthenia (14/16%), and neurotoxicity (11/16%). There were no significant differences in 6 months OS 63/69%, response rate (RR) 24/28% and median progression free survival (PFS) 5.7/6.7 months respectively in each arm.

Results: Regimens arm C and arm E (days 1, 8, 15 every 28 days schedule) were selected for the phase 2 portion of the study. A total of 221 patients (111 in arm C/110 in arm E) were enrolled. Median age was 71/68 y, 51/55% were male and 91/83% had metastatic PDAC (Von Hoff et al, 2013). The aim of this study was to select a tolerable dose-schedule of nab-P + G (Ph I), and to evaluate the efficacy of the selected regimen (Ph II) in patients with previously untreated ECOG 2 advanced PDAC.

Methods: In the phase I portion of the study patients were randomized to one of 6 treatment regimens including G 1000 mg/m2 and nab-P 150 mg/m2 (arm B) or 125 mg/m2 (arm D) days 1 and 15 every 28 days or same dose of G and nab-P 100 mg/m2 (arm C) or 125 mg/m2 (arm E) days 1, 8, and 15 every 28 days. The two safest regimens determined by analyzing hematological and non-hematological grade 3-4 toxicity, 30 and 60 days mortality, treatment discontinuation due to toxicity and dose intensity were selected for evaluation in the phase 2 portion of the study with 6 months overall survival (OS) as the primary endpoint.

Results: A phase I and randomized phase II trial to evaluate the efficacy and safety of nab-paclitaxel (nab-P) in combination with gemcitabine (G) for the treatment of patients with ECOG 2 advanced pancreatic cancer (PDAC)
Muparfostat showed a significant prolongation in the disease-free time after completion of 52 weeks of treatment. After subgroup analysis on proteins identified as significant for OS and TTP, interaction analysis suggested that a high protein concentration was associated with a response to REG treatment in patients with microvascular invasion. Five proteins were predictive for TTP in the REG group. Although subgroup analysis revealed that the predictive effect of muparfostat was independent of REG treatment benefit, multiple proteins were identified as potentially predictive for REG clinical benefit (OS and TTP) in RESORCE. Additionally, the exploratory analysis suggests that most patients with HCC derived benefit from REG treatment, multiple proteins were identified as potentially predictive for REG clinical benefit (OS and TTP) in RESORCE.

Conclusion: The overall and biomarker cohorts were similar for demographic variables and outcomes. Five proteins were predictive for OS (Table), but were not prognostic. 47 proteins were predictive for TTP (6 were prognostic) and included the 5 proteins predictive for OS in general. The REG treatment benefit for OS was maintained in dichotomized, quartile, and STEPP subgroup analyses, with lower protein levels correlating with improved treatment benefit. However, composite scores integrating information across predictive proteins indicated that in a small group of putative high-risk proteins, high protein concentration was associated with a response to REG treatment. The predictive and prognostic effects of REG treatment benefit were modeled as a protein–treatment interaction effect and subjected to Akaike information criterion (AIC)-based selection to assess the association of protein and REG treatment benefit. Subgroup analysis was done on proteins identified as significant for both OS and TTP to generate a patient-wise protein composite score.

Results: The overall and biomarker cohorts were similar for demographic variables and outcomes. Five proteins were predictive for OS (Table), but were not prognostic. 47 proteins were predictive for TTP (6 were prognostic) and included the 5 proteins predictive for OS in general. The REG treatment benefit for OS was maintained in dichotomized, quartile, and STEPP subgroup analyses, with lower protein levels correlating with improved treatment benefit. However, composite scores integrating information across predictive proteins indicated that in a small group of putative high-risk proteins, high protein concentration was associated with a response to REG treatment. The predictive and prognostic effects of REG treatment benefit were modeled as a protein–treatment interaction effect and subjected to Akaike information criterion (AIC)-based selection to assess the association of protein and REG treatment benefit. Subgroup analysis was done on proteins identified as significant for both OS and TTP to generate a patient-wise protein composite score.


Disclosure: P.-J. Chen: Honorarium from Medigen Biotechnology Corporation. K.-L. Lai: Employee of Medigen Biotechnology Corporation. All other authors have declared no conflicts of interest.

Table 625PD

<table>
<thead>
<tr>
<th>Protein</th>
<th>REG-predictive effect on OS, HR (95% CI)</th>
<th>Interaction P-value</th>
<th>Adjusted interaction P-value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOX-1</td>
<td>1.35 (1.16, 1.57)</td>
<td>&lt;0.001</td>
<td>0.009</td>
<td>1 ng/mL increase</td>
</tr>
<tr>
<td>ANG-1</td>
<td>1.12 (1.05, 1.19)</td>
<td>&lt;0.001</td>
<td>0.019</td>
<td>1 ng/mL increase</td>
</tr>
<tr>
<td>Cystatin-8</td>
<td>1.46 (1.15, 1.85)</td>
<td>0.002</td>
<td>0.040</td>
<td>2-fold increase</td>
</tr>
<tr>
<td>LAP TGF-beta 1</td>
<td>1.36 (1.12, 1.65)</td>
<td>0.002</td>
<td>0.040</td>
<td>2-fold increase</td>
</tr>
<tr>
<td>MIP-1alpha</td>
<td>1.02 (1.01, 1.04)</td>
<td>0.002</td>
<td>0.040</td>
<td>1 pg/mL increase</td>
</tr>
</tbody>
</table>

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doi:10.1093/annonc/mdx369 | 113
A randomized phase III trial comparing 4 courses and 8 courses of S-1 adjuvant chemotherapy for p-stage II gastric cancer: JCOG1104 (OPAS-1)


Background: Postoperative S-1 for 1 year (corresponding to 8 courses) is a standard adjuvant chemotherapy for p-stage II gastric cancer based on ACTS-GC phase III study comparing surgery alone and S-1. Duration of adjuvant chemotherapy for 1 year was continued until 6 months was established for colon cancer based on several phase III studies to compare duration. It remains unclear whether S-1 for 1 year could be shortened to 6 months (corresponding to 4 courses) without worsening the survival.

Methods: We conducted a multi-center phase III trial to confirm non-inferiority in relapse-free survival (RFS) of 4 courses S-1 to 8 courses S-1 in p-stage II gastric cancer. Key eligibility criteria were p-stage II except T1N0 and T3N0 (7th edition of TNM), performance status 0-1, R0 resection with D2 lymph node dissection for stage II or D1+ lymph node dissection for stage I, within 7 weeks after surgery, and age between 20 and 80 years. Primary endpoint was RFS and secondary endpoints included overall survival (OS), time to treatment failure (TTF), and adverse events. Patients were randomized into 4 course S-1 or 8 course S-1. 80 mg/m² of S-1 was administered for 4 weeks with a rest for 2 weeks as one course. Total sample size was determined to be 1,000 with 3-year RFS of 85% in both arms and non-inferiority margin of hazard ratio (HR) of 1.37, one-sided alpha of 5% and 80% power.

Results: Between Feb 2012 and Mar 2017, 590 patients were enrolled in this study. Among them, 528 patients were analyzed at the first planned interim analysis at Mar 2017. JCOG Data and Safety Monitoring Committee recommended early termination of the trial because the point estimate of HR was greater than non-inferiority margin of HR, which met the prespecified criteria for early stopping. The study was closed on the basis of futility. RFS at 3 years was 88.9% for 4-courses arm and 93.6% for 8-courses arm (HR 2.52, 95% CI 1.11-5.77). OS at 3 years was 91.7% for 4-courses arm and 95.3% for 8-courses arm. T stage of GC was 1 in 11 patients, 2 in 4, and 3 in 4. Of 19, 10 underwent endoscopic treatment, 5 underwent gastrectomy, 1 received chemotherapy, and 1 did not receive any anti-cancer treatment. The overall survival rates at 5 years in S group, SEC group, and AEC group were 50%, 45%, and 51%, respectively. There was a significant difference in the overall survival rates between the surgery group (45%) and non-surgery group (36%) in the SEC group (p = 0.0006). In the SEC group, there was a tendency of long survival in those who underwent surgery (56%), compared to those who did not have surgery (57%) (p = 0.08). Prognosis of patients with gastric tube cancer was 10 years after EC treatment and 4 years after gastric tube cancer treatment.

Conclusions: Patients in the S group who underwent surgery had a good prognosis. Periodic endoscopic examination is necessary for early diagnosis of gastric tube cancer.

Legal entity responsible for the study: Kanagawa Cancer Center Research and Development Fund

Funding: Japan Agency for Medical Research and Development and the National Cancer Center Research and Development Fund

Disclosure: All authors have declared no conflicts of interest.
The aim of this study was to clarify the optimal abdominal lymphadenectomy for Siewert type II and III esophagogastric junction carcinoma.

Methods: From June 2007 to June 2014, the data of 573 patients who underwent radical total gastrectomy due to advanced Siewert types II and III was collected and retrospectively analyzed. The incidence of abdominal lymph node metastasis (LNMs) of each station were compared between patients with Siewert type II and III AEG. And we used the therapeutic index to assess the efficacy of abdominal lymph node dissection of each station.

Results: Of the 573 patients, 247 (44.0%) had Siewert type II AEG and 326 (56.0%) had type III AEG. Among them, 252 patients carried out abdominal D2 lymphadenectomy and 321 patients underwent D2 lymphadenectomy without No. 10 lymphadenectomy.

Conclusions: Dissection of No. 1, 3, 7, 9 and 11 LNs would obtain highest survival benefits regardless of the Siewert subtype. Patients with type AEG, especially those with primary tumors invading the serosa layer, undifferentiated cancers and tumor size \( \geq 50 \text{mm} \) might obtain relatively higher survival benefits from No. 10 lymphadenectomy.

Legal entity responsible for the study: Changming Huang

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Conclusions: In patients with surgery after NCRT, pathologic prognostic factors (LV1 and PNI1) were significantly associated with the prognosis of advanced stages, whereas clinical prognostic factors (cCR, clinical stages and age) were of early stages. Although further studies are needed to validate the results of this study, we carefully suggest that clinical and pathological factors have a role in predicting survival outcome in detail based on ypTNM stage by stratifying each ypTNM stage into groups showing distinct survival profiles.

Legal entity responsible for the study: Asan Medical Center, Department of Oncology

Funding: None

Disclosure: All authors have declared no conflicts of interest.

633P

Endoscopic resection for Barrett’s esophagus: Uzbekistan experience

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Background: In the treatment of esophageal dysplasia, particularly Barrett’s esophagus, radical endoscopic resection (SRR) has shown its effectiveness. The purpose of this study was to evaluate the long-term results of treatment of Barrett’s esophagus dysplasia after a successful SRR.

Methods: Patients who received SRR for BE ≤ 5 cm with high-grade dysplasia (HG) or early cancer (EC) achieved complete elimination of intestinal metaplasia (CE-IM) and neoplasia (CE-neo). Primary outcomes: relapse of neoplasia (HG/EC), recurrence of dysplasia (including indefinite dysplasia) and recurrence of endoscopically visible BE. METHODS: Patients who received SRR for BE ≤ 5 cm with high-grade dysplasia (HG) or early cancer (EC) achieved complete elimination of intestinal metaplasia (CE-IM) and neoplasia (CE-neo). Primary outcomes: relapse of neoplasia (HG/EC), recurrence of dysplasia (including indefinite dysplasia) and recurrence of endoscopically visible BE.

Results: Hidden Barrett’s glands, IM in biopsy specimens obtained distal to the normal emerging neo-squamous columnar compound, the need for re-treatment, and sustained by CE-IM and CE-neo at the last follow-up endoscopy. RESULTS: 76 patients were included (65 men, mean age 66 years, median BE 23M). The median follow-up was 76 months. A repetition of neoplasia was observed in 1 patient 130 months of observation and was treated with medical surgery (annual frequency 0.22% per year of the patient’s observation). Four patients had recurrent dysplasia (0.87% per patient-year of follow-up). Twelve patients had recurrent endoscopically visible BE (1.9% per patient-year of follow-up). Most of the islands or lagoons were not detected in the endoscopic examination. Five patients were found to have one Barrett’s ulcer disease (1.1% per year of the patient’s observation), and 27 patients (5.9% per year of the patient’s observation) showed MI in biopsies only distal to the neo-squamous columnar junction was not reproduced in 56%. Repeated treatment was performed in 9 patients. CE-IM and CE-neo (including IM in the neo-squamous column) in the last endoscopic endoscopy were seen in 99% and 97% of patients, respectively.

Conclusions: This study presents the longest published data on SRR to date. 6-year results show that a successful SRR is a long-term therapy for BE ≤ 5 cm with HG/EC.

Legal entity responsible for the study: Tashkent Medical Academy

Funding: None

Disclosure: All authors have declared no conflicts of interest.

632P

Thromboembolic complications in patients with oesophageogastric adenocarcinoma undergoing preoperative chemotherapy

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Background: The scope of the present study was to: describe the incidence of thromboembolic events (TE) in patients (pts) with resectable oesophageogastric (OG) adenocarcinoma receiving preoperative chemotherapy (CT) with curative intent; to assess risk factors of developing TE; to determine their impact on patient outcome.

Methods: Data from 590 pts with OG adenocarcinoma, who received epirubicin, cisplatin and capcitabine (ECX) or 5-fluorouracil (ECF) preoperatively in 3 UK hospitals, between 2009 & 2016, were collected retrospectively.

Results: Median age was 66 years (range 28–85), 81% were males, 21% had gastric primaries, 98% received ECX chemotherapy, and 87% completed all 3 cycles of preoperative CT. In total, 52 pts (9%) had a venous and 22 (4%) an arterial event. Of patients with venous TE, 39 had pulmonary embolism and 13 deep vein thrombosis. Of patients with arterial TE (6), 3 had peripheral embolism, 1 limb ischemia, 4 cerebral/vascular accidents and 3 superior mesenteric artery thrombosis. Arterial TE was associated with much higher inoperability rate compared to cases with venous TE or without TE (77% vs. 31% vs. 20% respectively, p < 0.001). Primary tumour location in the stomach (Odds ratio [OR] 3.24, 95% CI 1.72–6.12, p < 0.001), overweight (OR 3.11, 95% CI 1.85–5.12, p = 0.001), age (OR 3.40, 95% CI 1.00–11.55, p = 0.049) and the presence of central venous access (OR 3.40, 95% CI 1.00–11.55, p = 0.049) were independent risk factors for venous TE development, while anticoagulant treatment was independently associated with a lower risk of venous TE (OR 0.22, 95% CI 0.06–0.83, p = 0.026). A very high Khorana score (of 4–5) was the only independent risk factor for arterial TE (OR 6.38, 95% CI 1.85–22.04, p = 0.003). Furthermore, arterial TE was an independent poor prognostic factor for OS when adjusted for baseline patient, tumour and treatment characteristics (Hazard ratio [HR] 3.02, 95% CI 1.85–4.95, p = 0.001).

Conclusions: Preoperative ECX/ECF chemotherapy for patients with resectable OG adenocarcinoma was associated with relatively high incidence of TE. However, only arterial TE affected patient outcome.

Legal entity responsible for the study: Wast Mansoor

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Table: 631P Subgroup analysis of 5-year OS according to ypTNM stage

<table>
<thead>
<tr>
<th>ypTNM Stage</th>
<th>5-year OS rate</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Age &lt; 65, clinical stage 1–2</td>
<td>85.8%</td>
</tr>
<tr>
<td></td>
<td>Age &lt; 65, clinical stage 3–6</td>
<td>76.9%</td>
</tr>
<tr>
<td></td>
<td>Age &gt; 65, clinical stage 1–2</td>
<td>71.5%</td>
</tr>
<tr>
<td></td>
<td>Age &gt; 65, clinical stage 3–6</td>
<td>44.7%</td>
</tr>
<tr>
<td>1 (including ypTNM-M0)</td>
<td>cCR</td>
<td>87.5%</td>
</tr>
<tr>
<td></td>
<td>non-cCR</td>
<td>41.2%</td>
</tr>
<tr>
<td>2</td>
<td>LV (+), PNI (+), cCR</td>
<td>66.7%</td>
</tr>
<tr>
<td></td>
<td>LV (+), PNI (+), non-cCR</td>
<td>39.1%</td>
</tr>
<tr>
<td></td>
<td>LV (+) and/or PNI (+)</td>
<td>0.0%</td>
</tr>
<tr>
<td>3</td>
<td>LV (+), PNI (+)</td>
<td>30.3%</td>
</tr>
<tr>
<td></td>
<td>LV (+) and/or PNI (+)</td>
<td>7.1%</td>
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</table>
635P Prognostic significance of local immunity factors in esophageal cancer
E.N. Kolesnikov1, O.I. Ne1, E.Y. Zlata2, A.L. Bazarev3, A.Y. Maksimov1, I.A. Novikova3, O.N. Setyutina1, E.S. Bandarenko1, V.S. Tifani2, L.V. Khan1, P.N. Gabrichide1, M.A. Kashushko1, S.S. Mefizren3, L.Y. Vladimirova3
1Department of Abdominal Oncology, Rostov Research Institute of Oncology, Rostov-on-Don, Russian Federation, 2Laboratory of Immunophenotyping of Tumors, Rostov Research Institute of Oncology, Rostov-on-Don, Russian Federation, 3Drug Therapy Department, Rostov Research Institute of Oncology, Rostov-on-Don, Russian Federation

Background: The purpose of the study was to assess possible prognostic significance of local immunity parameters in patients with esophageal cancer.

Methods: We studied tissues of tumor, peritumoral zone (PZ) and resection line (RL) obtained from 37 patients (11 women, 24 men aged 46–78 years) during surgical treatment of esophageal cancer with tumors located in the upper (1), mid (16), lower (19) thoracic esophagus and its abdominal part (1 patient). Histological study showed squamous cell carcinoma, keratinizing in 27 and non-keratinizing in 10 patients. Differentiation of tumors was G3, G2 and G1 in 7, 19 and 11 patients, respectively. The follow-up period lasted from 11 to 22 months. Patients received postoperative multi-course CF chemotherapy. Metastases in distant lymph nodes developed in 13 patients, metastases to paracardial organs in 6 patients; 7 patients died. 16 patients did not show signs of progression during the follow-up period. Subset of T, B and NK-lymphocytes were determined in homogenates of tissues obtained during surgery using the FACS®Cantoll flow cytometer (BD) with a panel of antibodies CD45, CD3, CD4, CD8, CD19, CD16/56; levels of T-regs (CD4 CD25+) – from the number of CD3+CD4+ cells. Results: The ratios of percentages of different lymphocyte subsets were compared in presence or absence of the disease progression during a follow-up period. The ratio of T-reg in PZ to the level in tumor in patients with further progression was 0.43±0.5 err. 0.3, while in patients without progression it was significantly lower – 0.15±0.033 (p < 0.05). The ratio of T-reg in PZ to the level in RL during a follow-up period in patients with progression was – 2.85±0.45, without progression – 0.57±0.126 (p < 0.05). On the contrary, the coefficient of CD3+CD8+ cells in RL to their level in tumor was lower in patients with progression (0.91±0.153) than in patients without it (1.33±0.32) (p < 0.05).

Conclusions: The ratios characterizing local immunity (PZ/tumor and PZ/RL for T-reg and RL/tumor for CD3+CD4+ lymphocytes) in patients with esophageal cancer proved to have prognostic significance for progression.

Legal entity responsible for the study: Rostov Research Institute of Oncology

Funding: None

Disclosure: All authors have declared no conflicts of interest.

636P Recent advance in enhanced recovery after esophagectomy: A systematic review and meta-analysis
T. Wang
Thoracic Surgery, 4th Hospital Hebei Medical University, Shijiazhuang, China

Background: Many studies have shown that enhanced rehabilitation after surgery (ERAS) protocol can be closely linked to the reduced hospital stay and better outcomes of cancer patients, including those with esophageal carcinoma. However, not all studies have generated encouraging results. Therefore, a systematic review and meta-analysis of recent advance evidence to evaluate the significance of ERAS following esophagectomy was conducted.

Methods: A literature search was performed in Medline, Embase, Pubmed, CINAHL, and the Cochrane library for articles describing an enhanced rehabilitation after surgery protocol in esophagectomy for esophageal cancer published between January 2010 and December 2016. The primary outcome measure was postoperative cardiac or pulmonary complication rates. Secondary outcome measures were postoperative length of stay, readmissions, and mortality. Statistical analysis was carried out using Comprehensive Meta Analysis 2.0.

Results: The literature search identified 118 potentially relevant papers. 12 papers met the inclusion criteria for the review: 7 case-control studies, 3 retrospective studies, and 2 prospective randomized controlled study, describing a total of 1,895 patients. Meta-analysis of six studies focusing on pulmonary complications showed that there was a significant difference in favor of the ERAS group (OR = 0.625, 95% confidence interval (CI) 0.479–0.815, p = 0.001; I²=9%). Implementation of an ERAS protocol led to a significant decrease in cardiac complications (OR = 0.606, 95% confidence interval (CI) 0.474–0.907, p = 0.011; I²=12.905%). Postoperative length of hospital stay was significantly shorter in ERAS group (standard mean difference = –0.208), 95% confidence interval = –3.202 to –0.913, P = 0.000; P for heterogeneity = 0.000. I²=109%). Introduction of an ERAS protocol did not result in an increase in anastomotic leak, chyle leak, mortality or readmissions. There was no significant difference in ICU stay and hospital cost.

Conclusions: ERAS protocol as compared with conventional procedure may reduce postoperative hospital stay and cardiac or pulmonary complication rates in patients undergoing esophagectomy for esophageal cancer.

Legal entity responsible for the study: 4th Hospital Hebei Medical University

Funding: None

Disclosure: All authors have declared no conflicts of interest.

637P High thromboembolic event rate in patients with locally advanced esophageal cancer during perioperative therapy: A pre-planned analysis of the intergroup phase III trial SAKK 75/08
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Background: High rates of venous thromboembolic events (VTE) are reported for patients (pts) with upper GI-cancers (stomach, pancreas) and treatment with Cisplatin (Cis), but mainly in retrospective analyses and in advanced disease. A prospective analysis of VTE in pts with resectable esophageal cancer is warranted.

Methods: Pre-planned analysis of VTE in a multicenter phase III trial according to reported AEIs and SAEs from start of preparative treatment until 6 months postoperatively. Pts with resectable esophageal cancer (T2N1-3, T3-4aNx) received 2 cycles of induction chemotherapy (CT) with Docetaxel (Doc) 75mg/m2, Cis 57mg/m2 followed by chemosimulation (CRT) with 45 Gy, Doc 20 mg/m2 and Cis 25 mg/m2 weekly then surgery or were randomly assigned to the same treatment with addition of neoadjuvant and adjuvant cetuximab.

Results: Of 300 pts 29 VTE were reported in 26 pts with an incidence rate (IR) of 8.7%. 3 pts had VTE 72% (21/29) of all VTE occurred preoperatively. No significant difference between treatment arms was found, odds ratio (OR) 0.8 [95%CI 0.4–1.9], p = 0.7. Grades (G) of VTE according to CTCAE v4.0: 3% (129 G1), 41% (129 G2), 45% (13/ 29) G3 and 10% (3/29) G5. In a multivariable logistic regression including baseline hemoglobin, platelets, neutrophils, BMI, treatment arm and histology, only adenocarcinoma (IR 11.2%, 21/189) compared to squamous cell cancer (IR 4.5%, 5/111) was significantly associated with VTE-risk during treatment, OR 2.9 [95%CI 1.02;8.4], p = 0.046. Baseline hK-Ras score (RKS) for VTE was 0.279 (19/29), 1.2 in 23% (6/26) of pts and 3 in one patient with VTE (≥3 equal to high-risk and recommenda- tion for prophylaxis). Median PPS in pts with VTE was 2.1 yrs vs 2.5 yrs for pts without VTE.

Conclusions: This first prospective analysis of VTE in resectable esophageal cancer pts reveals a high IR during perioperative therapy of almost 9% comparable to high-risk pts according to RKS. Only one of these pts would have been identified by RKS as high-risk. Prophylactic anticoagulation balanced against individual bleeding risks could be considered in esophageal cancer pts treated with neoadjuvant Cis-based CT and CRT, especially in adenocarcinoma.

Clinical trial identification: NCT 01107639 (release date: April 20, 2010)

Legal entity responsible for the study: Swiss Group for Clinical Cancer Research (SAKK)

Funding: Merck KGaA, Darmstadt, Germany

Conclusions: Nivo suggest a durable, long-term survival benefit with 17.2% of patients cough (12.3%). Seven patients (10.8%) discontinued the study treatment due to drug-treatment by 89.5% and 87.5%, respectively. Flow cytometry decreased with treatment by 89.5% and 87.5%, respectively. Flow cytometry decreased (5%). No treatment related death was observed. Results: A total of 42 patients were enrolled. 90% of the patients were male, 95% had distant metastasis, and 98% had target lesion (s). As of data cutoff, 34 events were observed. PFS3 was 15.4% (90% CI 7.4%, 26.0%), which did not reject the null hypothesis. Median PFS and OS were 13.3 months and 4.5 months, respectively. Response rate was 0%, although 24% (10/42) of patients achieved stable disease. There were 3 patients not evaluable for response. Major treatment related adverse events of grade ≥3 were: neutrophil count decreased (44%), febrile neutropenia (7%), and appetite decreased (5%). No treatment related death was observed.

Conclusions: TAS-102 was feasible and showed modest efficacy in patients with refractory/intolerable to standard therapies.

Clinical trial identification: JapicCTI-No.142422

Clinical trial identification: UMIN000019280, 2015/10/13

Dual CDK 4/6 inhibitor demonstrates potent antitumor efficacy in vitro and in vivo against esophageal adenocarcinoma

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Background: Esophageal adenocarcinoma (EAC) is a leading cause of cancer deaths, and current treatment options are limited. Cell cycle regulators CDK4 and CDK6 are progressively upregulated in EAC carcinogenesis and associated with poor prognosis. The modified Levat model of esophageal adenocarcinoma (EAC) has demonstrated well-documented utility for in vivo efficacy testing against de novo EAC. In the present study, we evaluate a dual CDK4/6 inhibitor, abemaciclib, for the treatment of EAC.

Methods: Human EAC cell lines, OE33 and FLO1, were used to evaluate proliferation and apoptosis using BrDU and flow cytometry, respectively. E1 was performed on Sprague-Dawley rats to induce gastroduodenoesophageal reflux and the subsequent development of EAC. At 36 weeks post-operatively, rats were randomized to receive IP abemaciclib at 26 mg/kg per day or placebo for Administration of the CDK4/6 inhibitor. Drug efficacy was evaluated with MRI, endoscopic biopsy, gross histological evaluation, and CDK4/6 pathway expression by RT-PCR.

Results: With an established ED50 of 6µM in OE33 and 14µM in FLO1, proliferation decreased with treatment by 89.9% and 87.9%, respectively. Flow cytometry
demonstrated an increase of apoptosis by 45.6% and 38.9%, respectively. Twenty of 23 (87.0%) treated animals and all of 18 (100%) control animals reached study endpoint. Treatment group mortality consisted of rats afflicted with moderate peritonitis, diarrhea, and weight loss. Mean MBI tumor volume decreased by 151.0% in treatment animals and increased by 108.3% in control animals (p < 0.01). Treatment with abemaciclib demonstrated tumor volume increase in 0% (control = 66.7%) (p < 0.01), decrease in 79% (control = 0%) (p < 0.01), and stable volume in 21.1% (control = 33.3%) (p = 0.41). EAC prevalence in treatment animals decreased by 48.2%, whereas prevalence in control animals increased by 5.5% (p < 0.01). mRNA expression, pre- and post-treatment, demonstrated significant downregulation of CD46, CDK6, RBL1, pRB, and Cyclin D (p < 0.001).

Conclusions: Abemaciclib exhibits potent in vitro and in vivo antitumor efficacy in EAC models, providing the rationale for future clinical testing.

Legal entity responsible for the study: Eli Lilly and Co.

Funding: Eli Lilly and Co.

Disclosure: R.J. Kelly, A.H. Zaidi: Grant funding: Eli Lilly and Co. All other authors have declared no conflicts of interest.

641P The influence of body composition on the systemic exposure of paclitaxel in esophageal cancer patients

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Background: Weight loss and malnutrition are common symptoms of esophageal cancer, which can lead to skeletal muscle wasting and loss of adipose tissue. It was hypothesized that the pharmacokinetics (PK) of chemotherapy may depend on body composition (Prado et al, 2013). In addition, we earlier showed that the clearance (CL; L/h) of unbound paclitaxel (pac) is related to body-surface area (BSA; m²) and gender (Bins et al, 2014). Therefore, now we aim to assess the relationship between pac CL and body composition.

Methods: We analyzed 197 patients with stage III esophageal cancer who were treated with pac and carboplatin in a prospective study between 2008 and 2013. CL of pac, measured at the level of the 3rd lumbar vertebra on computed tomography (CT) scans performed before treatment. Gender-specific differences in pac CL, based on the 1st quartile and the 4th quartile of the SMI and VAT measurement were analyzed with a NONMEM model, which can lead to skeletal muscle wasting and loss of adipose tissue. It was hypothesized that the pharmacokinetics (PK) of chemotherapy may depend on body composition (Prado et al, 2013). In addition, we earlier showed that the clearance (CL; L/h) of unbound paclitaxel (pac) is related to body-surface area (BSA; m²) and gender (Bins et al, 2014). Therefore, now we aim to assess the relationship between pac CL and body composition.

Results: CL images and pac PK data were available for 183 patients (78% was men). Pac CL was correlated with SMI (r = 0.17, p = 0.001) and VAT (r = 0.28, p = 0.001), while no correlation was found with MA (r = 0.17, p = 0.09). Interestingly, while in male patients with the highest SMI a higher pac CL was found compared to the lowest SMI (p = 0.024), and also for the 1st and 4th quartile of VAT (p = 0.003), in female patients no effect of SMI and VAT on pac CL was seen.

Conclusions: Skeletal muscle mass and visceral adipose tissue are positively correlated with pac CL in male patients with esophageal cancer. Differences in body composition between men and women may potentially explain the difference in the outcome of this analysis, and may also partly explain the difference in pac CL between genders. Although the effect sizes are too small to support dose adaptations based on VAT or SMI, these parameters partly explain the large interpatient variability in pac PK.

Legal entity responsible for the study: Erasmus MC Cancer Institute

Funding: None

Disclosure: All authors have declared no conflicts of interest.

642P Survival in advanced oesophagogastric adenocarcinoma (OGA) improves with the use of multiple lines of therapy: Results from an analysis of over 500 patients (pts)

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Background: Palliative chemotherapy (CT) remains the primary mode of treatment for advanced OGA and is shown to improve survival in the 1st and 2nd line setting. We sought to evaluate the use of systemic therapy and assess survival outcomes for pts with advanced OGA treated at the Royal Marsden Hospital (RMH).

Methods: Retrospective analysis of consecutively treated pts receiving at least 1 cycle of CT for advanced OGA at RMH between April 2009 - Nov 2015.

Results: 511 pts were identified; 75% male, 25% female; median age at diagnosis 66 yrs (range 24-90). Treatment intent at initial diagnosis was radical in 21% (with subsequent relapse) and palliative in 79%. There was no significant difference in median overall survival (OS) in the advanced setting between pts with relapsed disease after initial radical treatment and pts with metastatic disease at diagnosis (12.6 vs 11.3m; p = 0.10). OS was significantly improved for confirmed HER2+ ve pts compared to HER2- ve (15.0 vs 11.9m; p = 0.02). OS was significantly improved in pts treated within a therapeutic clinical trial at any line of treatment compared with those who were not (13.5 vs 10.1m; p = 0.02). Survival was significantly correlated with number of treatment lines received (p < 0.001).

Conclusions: We have demonstrated the pattern of usage of systemic therapy for over 500 patients treated within a single UK oncology centre. Survival outcome remains poor for the majority of pts who have 1st line CT only. Pts suitable for sequential CT have better outcomes and entry into clinical trials is associated with improved survival. There remains a need to define evidence-based therapies for the small but increasing proportion of pts suitable for treatment in the 3rd line and beyond.

Legal entity responsible for the study: Dr N Starling, Royal Marsden Hospital NHS Foundation Trust, Gastrointestinal medical oncology unit.

Funding: None

Disclosure: I. Chau: Sanofi Oncology, Eli Lilly, Bristol-Meyers Squibb, MSD, Bayer, Roche, Five Prime Therapeutics, Janssen, Glaxo, Sanofi, Merck Serono, Novartis, Taiho, Pfizer, Amgen, Aigile. D. Cunningham: Amgen, AstraZeneca, Bayer, Celgene, Merrimack, Medimmune, Merck Serono, Sanofi All other authors have declared no conflicts of interest.

Table: 642P

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<th>OS (m)</th>
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<td>ORR</td>
<td>PFS (m)</td>
<td>OS (m)</td>
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<td>11.5 (whole cohort)</td>
<td>3.0</td>
<td>14.0 (1st &lt; 2nd line received)</td>
<td>20.1 (1st &lt; 2nd &lt; 3rd line received)</td>
<td>33.0 (&gt; 3 lines received)</td>
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</tbody>
</table>

References:

Methods: Between September 2012 and December 2016, 420 patients with clinical stage IIA-IIIC gastric cancer were eligible for inclusion. They were randomly assigned to either the neoadjuvant chemotherapy group (n = 210) or the adjuvant chemotherapy group (n = 210). The reaction rate, effective rate, and CCI rate were 46%, 40% and 20% respectively. The surgical R0 resection rate (80 vs 70%) was significantly higher in neoadjuvant chemotherapy group. There was no significant difference in incidences of adverse reaction between the two groups. However, the CCI rate (9% vs 8%) was lower and T-stage was earlier in neoadjuvant chemotherapy group.

Conclusions: S-1 and oxaliplatin as neoadjuvant chemotherapy is effective for advanced gastric cancer, and there was no increase of adverse reaction.

Clinical trial identification: NCT01583361, April 4, 2012

Legal entity responsible for the study: Lin Chen

Funding: National Natural Science Foundation of China and Beijing Nova program

Disclosure: All authors have declared no conflicts of interest.

Open Peer Review:

Irit Ben-Aharon

Abstract:

The N stages for early gastric cancer should differ from those of advanced gastric cancer: Results based on the SEER database

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Background: The aim of this study was to establish an appropriate N staging system for early gastric cancer (EGC).

Methods: Data from 24,223 patients who underwent radical gastrectomy between 1988 and 2011 were retrieved from the National Cancer Institute’s Surveillance, Epidemiology, and End Result (SEER) database. The optimal cutoff value for the number of LNs was determined by the X-tile program. The overall survival (OS) based on eighth edition and new TNM staging systems were compared, and the analysis was repeated in an external validation set.

Results: In the same T category, the OS rates were significantly different in each N category for advanced gastric cancer (AGC). However, no significant differences were observed in OS between N1 and N2 cancers or between N3a and N3b cancers in cases of EGC. The X-tile program identified that the difference in survival was most significant when 6 metastatic LNs were present. The new staging system for EGC consisted of T1N0, T1N11 (1–6 metastatic LNs) and T1N21 (≥7 metastatic LNs). Compared with the eighth edition of the TNM staging system, the OS of patients in the T1N11 stage was similar to that of patients with stage IIA disease, whereas the OS of patients in the T1N21 stages was similar to that of patients with stage IIB disease (P < 0.05). The new TNM staging system exhibited slightly superior prognostic stratification with lower AIC values and higher χ2 and c-statistic compared with the eighth edition of the TNM classification system. Similar results were found in the external validation dataset from the Fujian Medical University Union Hospital (FMUHH) database.

Conclusions: The N category of the eighth edition of the AJCC-TNM classification exhibits variation in the survival of patients with AGC. However, this classification remains associated with some stage migration in EGC and the proposed N category permits better prognostic prediction.

Legal entity responsible for the study: Changming Huang

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Open Peer Review:

Young-onset gastric cancer: The role of microbial factors

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Oncology, Rabin Medical Center, Petach Tikva, Israel, 2Cell Biology, Tel-Aviv University, Tel-Aviv, Israel

Background: Gastric cancer (GC) is a leading cause of cancer death, associated with environmental and genetic factors, with increasing incidence in young patients. Recently, as part of the Cancer Genome Atlas (TCGA) project, a comprehensive molecular characterisation of gastric adenocarcinoma revealed unique molecular and genetic patterns that were classified GC into four subtypes among which is the Epstein-Barr Virus (EBV)-associated subtype. The EBV-associated subtype is positive for the virus, displays unique genomic landscape and represents 8.7% of the cohort of the TCGA. Since most of the young-onset GC is sporadic and non-hereditary upon former studies, environmental and genetic factors may play a role in the pathogenesis of GC among young patients. We hypothesized that the prevalence of EBV-subtype may be higher in young-onset GC than in the average-onset.

Methods: Tissue tumor samples of matched cohorts of young-onset (<45y) and average-onset (>60y) were retroprospectively retrieved, DNA was extracted and analyzed by quantitative PCR (qPCR) for EBV using two different EBNA primers to validate the detection of the virus. Clinical data among which are the anatomopathological data, tumor location and family history were extracted from medical records and correlated to age.

Results: Twenty-nine young-onset GC patients and 34 average-onset GC patients were enrolled into the study. Median age for the young-onset was 34y (range 21–45) and for the average-onset 69y (60–90). Thirty-six percent of the young-onset were male, comparing with 57% in the average-onset. Family history was more prevalent in the young-onset cohort (37% vs. 29%). The distribution of the tumor location differed between the two groups— whereas in the young-onset 36% of the tumors were in the body of the stomach compared with 46% of the average-onset that were in the antrum. EBV was significantly more prevalent in the young-onset cohort (32.1% compared with 11.4% in the average-onset).

Conclusions: Our study indicate that EBV may play a key role in the pathogenesis of young-onset GC. Since young-onset GC is not predominated by hereditary factors, environmental and microbial factors should be further studied as essential contributors, what may potentially govern early detection in high risk populations.

Legal entity responsible for the study: Irit Ben-Aharon

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Open Peer Review:

Comprehensive classification index (CCI) predicts cancer-specific survival of patients with neoadjuvant chemotherapy after curative resection of gastric cancer

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Background: To investigate prognostic impact of postoperative complications for patients with gastric cancer.

Methods: Postoperative complications of patients undergoing radical gastrectomy for gastric cancer were reviewed. The severity of complications was graded by the CCI and C-D classification.

Results: A total of 3327 patients were included in the study. Complications were observed in 767 patients. When the C-D classification system was applied, for patients with grade I-II complications, the length of stay (LOS) of those with high CCI (CCI ≥ 26.2) was significantly longer than that of patients with low CCI (CCI < 26.2) (p < 0.001). The 5-year cancer-specific survival rate of the patients with complications (52%) was lower than that of patients without complications (61%) (p < 0.001). Analysis of the factors associated with prognosis in patients with gastric cancer revealed that complications were independent risk factors for specific survival. When CCI was used to classify complication severity, the 5-year cancer-specific survival rate of the high CCI group was 46.3%, which was lower than that of the low CCI group (54.9%, p = 0.009).

Conclusions: Complication after radical gastrectomy is an independent prognostic factor, and the complication severity as graded by CCI reflects the difference of cancer-specific survival in gastric cancer patients with postoperative complications.

Legal entity responsible for the study: Changming Huang

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Open Peer Review:

ATM loss, MSI and survival in the MAGIC trial

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Background: Loss of ataxia-telangiectasia mutated (ATM) protein has been associated with worse prognosis in resected gastric cancer (GC), and may predict sensitivity to drugs targeting DNA damage pathways. Microsatellite instability (MSI) is prognostic in surgically treated GC patients (pts) and may be negatively prognostic in perioperative chemotherapy (chemo) treated GC. We examined the effect of ATM and MSI on overall survival (OS) for pts randomised to surgery alone or perioperative ECF chemo in the MRC MAGIC trial.

Methods: ATM was assessed using anti-ATM antibody (clone Y170) on 4 μm TMA sections. ATM negative (neg) tumours had >90% cells neg for ATM at nuclear level. MSI was assessed using Promega MSI system. MSI tumours had all markers stable; MSI-L had only 1 unstable marker; MSI-H had at least 2 unstable markers. Trial arms were analysed independently.

Results: 39 of 225 evaluated pts (17%) were ATM-neg. Pts with/without ATM data had similar OS. Clinicopathological characteristics were similar between ATM-neg and positive (pos) pts. 217 pts had MSI and ATM status available: MSI and ATM status were highly correlated (ATM-neg/MSI-H = 27, ATM pos/MSI-H = 10, ATM-pos/MSI-L = 17, ATM-pos/MSI-MI-H = 5, p < 0.001). Median OS for all biomarker groups is detailed in the table.
NLN count

Methods: Surveillance, Epidemiology, and End Results Program (SEER)-registered gastric cancer patients were used for analysis in this study. Kaplan–Meier survival curves and multivariate Cox proportional hazards model were used to assess the risk factors. The risk score of NLN counts demonstrated that the plot of hazard ratios (HRs) for the risk factors in various cancers after radical resection. However, the prognostic value of NLN count in the setting of gastric cancer patients who have received palliative resection has not been investigated. The aim of the present study was to explore the effect of NLN counts on the survival outcomes in patients with stage IV gastric cancer after palliative resection.

Background: Negative lymph node (NLN) count has been validated as a protective pre- dictor in various cancers after radical resection. However, the prognostic value of NLN counts in the setting of gastric cancer patients who have received palliative resection has not been investigated. The aim of the present study was to explore the effect of NLN counts on the survival outcomes in patients with stage IV gastric cancer after palliative resection.

Methods: Surveillance, Epidemiology, and End Results Program (SEER)-registered gastric cancer patients were used for analysis in this study. Kaplan–Meier survival curves and multivariate Cox proportional hazards model were used to assess the risk factors for survival.

Results: A total of 1,493 patients with stage IV gastric cancer underwent palliative resection were identified from SEER database between 2004 and 2011. It showed that NLN count (P < 0.001) and N stage (P < 0.001) were independently prognostic factors in patients with stage IV gastric cancer after palliative surgery. X-tile plots identified 2 and 11 as the optimal cutoff values to divide the patients into high, middle and low risk subgroups in term of cause-specific survival (CSS). And NLN count was proved to be an independently prognostic factor in multivariate Cox analysis (P < 0.001). There was a significant correlation between TC and IC PD-L1 expression in primary tumours (P < 0.001) but not in metastases. There was no significant association between TC PD-L1 expression in primary tumours and metastases, but IC PD-L1 expression was significantly higher in metastases (P = 0.027). There were strong significant associations between PD-L1 expression in TC and IC, respectively, and MSI status (P < 0.001 for both). Neither PD-L1 expression nor MSI status was prognostic. However, high IC PD-L1 expression (>50%) was significantly associated with a prolonged OS, independent of conventional prognostic factors and MSI status (HR = 0.39, 95% CI 0.15–0.99).

Conclusions: Our present study revealed that NLN count was an independent prognostic factor in stage IV gastric cancer after palliative resection. Standard lymph node dissection, such as D2 lymphadenectomy maybe still necessary during palliative resection for patients with metastatic gastric cancer.

Legal entity responsible for the study: N/A

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Table: 647P Overall survival (OS) by ATM, MSI and treatment arm

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Events</th>
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<th>95% CI for Median OS</th>
<th>HR</th>
<th>95% CI for HR</th>
<th>Cox PH test</th>
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<tr>
<td>Surgery alone arm: OS from surgery by ATM status</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>ATM neg</td>
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<td>10</td>
<td>48.3</td>
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<td>Chemotherapy + surgery arm: OS from surgery by ATM status</td>
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<td>Chemotherapy + surgery arm: OS from surgery by ATM and MSI status</td>
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Conclusions: In MAGIC, ATM status was not prognostic for OS in either treatment arm. ATM loss was much more common in MSI-H pts than in all other subgroups. The relationship underpowered analysis, chemo treated MSS-ATM neg pts had encouraging OS. In chemo treated pts, prognosis was poor for MSI-H patients independent of ATM status. Further evaluation of ATM, CHEM and chemotherapy outcomes may be justified.

Legal entity responsible for the study: Medical Research Council

Disclosure: E. Smyth: Honoraria for advisory role; Five Prime Therapeutics, Bristol- Meyer Squibb. C. Peckitt: Honoraria for consulting or advisory role from Sanofi. W. Allum: Honoraria from Nestle and Lilly. D. Cunningham: Research funding: Amgen, AstraZeneca, Celgene, MedImmune, Merck-Serono, Merrittack, Sanofi. All other au- thors have declared no conflicts of interest.

468P Negative lymph node count is a significant prognostic factor in patients with stage IV gastric cancer after palliative gastrectomy

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Background: Negative lymph node (NLN) count has been validated as a protective predictor in various cancers after radical resection. However, the prognostic value of NLN count in the setting of gastric cancer patients who have received palliative resection has not been investigated. The aim of the present study was to explore the effect of NLN counts on the survival outcomes in patients with stage IV gastric cancer after palliative resection.

Methods: Surveillance, Epidemiology, and End Results Program (SEER)-registered gastric cancer patients were used for analysis in this study. Kaplan–Meier survival curves and multivariate Cox proportional hazards model were used to assess the risk factors for survival.

Results: A total of 1,493 patients with stage IV gastric cancer underwent palliative resection were identified from SEER database between 2004 and 2011. It showed that NLN count (P < 0.001) and N stage (P < 0.001) were independently prognostic factors in patients with stage IV gastric cancer after palliative surgery. X-tile plots identified 2 and 11 as the optimal cutoff values to divide the patients into high, middle and low risk subgroups in term of cause-specific survival (CSS). And NLN count was proved to be an independently prognostic factor in multivariate Cox analysis (P < 0.001). There was a significant correlation between TC and IC PD-L1 expression in primary tumours (P < 0.001) but not in metastases. There was no significant association between TC PD-L1 expression in primary tumours and metastases, but IC PD-L1 expression was significantly higher in metastases (P = 0.027). There were strong significant associations between PD-L1 expression in TC and IC, respectively, and MSI status (P < 0.001 for both). Neither PD-L1 expression nor MSI status was prognostic. However, high IC PD-L1 expression (>50%) was significantly associated with a prolonged OS, independent of conventional prognostic factors and MSI status (HR = 0.39, 95% CI 0.15–0.99).

Conclusions: Our present study revealed that NLN count was an independent prognostic factor in stage IV gastric cancer after palliative resection. Standard lymph node dissection, such as D2 lymphadenectomy maybe still necessary during palliative resection for patients with metastatic gastric cancer.

Legal entity responsible for the study: N/A

Funding: None

Disclosure: All authors have declared no conflicts of interest.

648P PD-L1 expression in primary tumours and paired lymph node metastases in chemoradiotherapy-naive oesophageal and gastric adenocarcinoma: Relationship with MSI status and prognosis

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Background: Although neoadjuvant and/or adjuvant treatment enhances survival in patients with resectable oesophageal and gastric (EG) cancer, the prognosis remains poor and there is a great need to identify novel treatment strategies and suitable bio-markers. The efficacy of immune-modulating therapies in EG cancer remains to be confirmed. Expression of programmed death ligand 1 (PD-L1) in EG cancer, the prognosis remains poor and there is a great need to identify novel treatment strategies and suitable bio-markers. The efficacy of immune-modulating therapies in EG cancer remains to be confirmed. Expression of programmed death ligand 1 (PD-L1) in EG cancer, the prognosis remains poor and there is a great need to identify novel treatment strategies and suitable bio-markers.

Methods: PD-L1 expression in primary tumours and paired lymph node metastases in chemoradiotherapy-naïve esophageal and gastric (EG) adenocarcinoma was assessed by immunohistochemistry (IHC) on tissue microarrays with primary tumours (n = 165) and paired lymph node metastases (n = 61) from a retrospective consecutive cohort of patients with chemoradiotherapy-naïve resected EG cancers. MSI was defined as loss of HIC expression of MLH1, MSH2, MSH6 or MSH3. Univariable and multivariable Cox regression analysis was used to calculate overall survival (OS).

Results: There was a significant correlation between TC and IC PD-L1 expression in primary tumours (p < 0.001) but not in metastases. There was no significant association between TC PD-L1 expression in primary tumours and metastases, but IC PD-L1 expression was significantly higher in metastases (p = 0.027). There were strong significant associations between PD-L1 expression in TC and IC, respectively, and MSI status (p < 0.001 for both). Neither PD-L1 expression nor MSI status was prognostic. However, high IC PD-L1 expression (>50%) was significantly associated with a prolonged OS, independent of conventional prognostic factors and MSI status (HR = 0.39, 95% CI 0.15–0.99).

Conclusions: PD-L1 expression in TC does not differ significantly between primary tumours and lymph node metastases, PD-L1 expression in IC but not in TC is an independent favourable prognostic factor.

Legal entity responsible for the study: Lund University

Funding: This study was supported by grants from the Swedish Cancer Society, the Swedish Research Council, the Mrs. Beta Kamprad Foundation, the Swedish Government Grant for Clinical Research (ALF), Lund University Faculty of Medicine, and the Lund University Hospital Research Grants.

Disclosure: All authors have declared no conflicts of interest.

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650P Effects of preoperative malnutrition on short- and long-term outcomes of patients with gastric cancer: Can we do better?

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Background: This study aimed to examine the effect of preoperative nutritional status on short- and long-term outcomes in patients who underwent radical gastrectomy. It also explored the role of preoperative correction of hypoaemia (PCH) in malnourished patients with gastric cancer.

Methods: We prospectively reviewed data from patients with gastric cancer who were treated in our department between January 2009 and December 2014. The effect of preoperative nutritional status on short- and long-term outcomes in patients who underwent radical gastrectomy was investigated. We explored whether PCH could improve the short- and long-term outcomes of these patients.

Results: A total of 1,976 patients were analyzed, including 412 in the malnourished group and 1,564 in the well-nourished group. The overall incidence of complications in the malnourished group was significantly higher than that of the well-nourished group (21.4% vs 15.9%, p = 0.005). Except for incision infection (3.2% vs 1.6%, p = 0.041), there were no significant differences for other complications. In the malnourished group, 98 cases of postoperative hypoaemia were corrected (PCH group), whereas 314 cases were not (NPCH group). The incidence of incision infection in the PCH group was significantly lower than that in the NPCH group (9%/vs 4.1%, p = 0.014). The median follow-up time was 39 months (1.0-8.8 months). The 3-year overall survival (OS) in the NPCH group was 83.7% (90.0% vs 89.0%, p = 0.027) and disease-free survival (DFS) in the PCH group was 72.5% (p = 0.001) vs 61.2% (p = 0.027) in the NPCH group. Among 314 cases of postoperative hypoaemia, 198 cases of preoperative hypoproteinemia were corrected (PCH group), whereas 116 cases were not (NPCH group). The incidence of incision infection in the PCH group was significantly lower in the NPCH group in the case of hypoaemia.

Conclusions: The incidence of incision infection was significantly higher in patients with malnutrition than in well-nourished patients. The 3-year OS and DFS were significantly lower in malnourished patients than in well-nourished patients. PCH can both reduce the incidence of incisional infection in patients with malnutrition and significantly improve the 5-year OS and DFS for malnourished patients with stage III/II gastric cancer.

Legal entity responsible for the study: Changhai Huang

Funding: None

Disclosure: All authors have declared no conflicts of interest.

651P Is there any relationship between Helicobacter pylori infection and HER2 expression in gastric cancer?

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2Medical Oncology, Department of Medical Oncology, Sakarya Education and Research Hospital, Sakarya, Turkey
3Pathology, Department of Pathology, Gazi University Faculty of Medicine, Ankara, Turkey
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5Medical Oncology, Department of Internal Medicine, Division of Medical Oncology, Gazi University Faculty of Medicine, Ankara, Turkey

Background: Helicobacter pylori (HP) is a significant causative agent of gastric cancer (GC). However, the underlying mechanisms involved in its pathogenesis and association with oncogenes are unclear. The aim of the present study was to evaluate the relationship between HP infection and human epidermal growth factor receptor 2 (HER2) expression in gastric cancer patients.

Methods: Surgery (175) or endoscopic biopsy (35) specimen of 210 patients diagnosed with GC was evaluated for the presence of HER2 and HP. HER2 expression was assessed by fluorescence in situ hybridization (FISH) method, whereas HP status was evaluated histologically. Gastric team was used to identify HP status, in case HP could not be recognized in routine hematoxylin eosin stained sections despite careful examination.

Results: The median age was 65 years (27-91) and most patients were male (male/female: 149/9). Histopathologic diagnosis was adenocarcinoma in 117 (56.2%), signet ring cell adenocarcinoma in 51 (24.6%), and mixed adenocarcinoma-signet ring cell adenocarcinoma in 40 patients (19.2%). Of all 210 patients, HP was positive in 87 (41.8%) and negative in 121 (58.2%) patients. FISH positivity for HER2 was observed in 41 (19.7%), whereas FISH negativity was observed in 167 (80.3%) patients. HER2 positivity was observed in 65 (30.9%) patients. In addition, there was no relationship between HP status and the age, gender, histopathologic diagnosis, tumor location, TNM stage, ECOG performance status, grade, lymphovascular invasion, perineural invasion, and Lauren classification. Median OS of the entire population was 14.8 months (0.07-82.5).

Conclusions: HER2 positivity was observed in 65 (30.9%) patients. In addition, there was no relationship between HP status and the age, gender, histopathologic diagnosis, tumor location, TNM stage, ECOG performance status, grade, lymphovascular invasion, perineural invasion, and Lauren classification. Median OS of the entire population was 14.8 months (0.07-82.5).

Median OS was 12.9 months (95% CI 7.7-18.0) in HP negative group and 27.4 months (95% CI 16.4-38.4) in HP positive group and the difference was statistically significant (p = 0.046).

Conclusions: Our results suggest that there is no relationship between HP infection and HER2 status in patients with GC. However, debate on this topic continues. Comprehensive prospective studies with larger series are required to clarify this relationship.

Legal entity responsible for the study: N/A

Funding: None

Disclosure: All authors have declared no conflicts of interest.

652P Iron deficiency anemia in gastric cancer: A Canadian single site retrospective cohort study

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Background: Globally, gastric cancer is highly prevalent amongst men and women. While many studies have identified the prevalence and association of iron deficiency anemia (IDA) in all cancer patients, few have focused on the gastric population. We aimed to determine the proportion of patients with gastric cancer who developed IDA, chemotheraphy induced anemia (CIA), and to identify types and frequencies of IDA therapies.

Methods: A retrospective study was carried out in 127 consecutive gastric cancer patients from 2006 to 2016 at St. Michael’s Hospital, Toronto, Canada. Patient demographics, previous history of IDA, and IDA-based therapies were reviewed. IDA was defined as hemoglobin (Hb) <130 g/L in men and <120 g/L in women and iron deficiency was defined as a transferrin saturation <20%. Pausalidation method was used for missing data. SAS 9.3 was used for data analysis.

Results: Of the 127 patients (median age 70 [interquartile range (IQR): 59-77]), 64.6% (82/127) were male. Most patients were diagnosed as stage I/II with a mean Hb of 119 g/L (standard deviation (SD): 20.2 g/L). Only 18.1% (23/127) patients had a history of IDA, 44.4% (54/121) had IDA at the time of gastric cancer diagnosis, and 59.1% (75/127) were anemic. Of the 127 patients, 16.5% had open surgery, while 45.7% had laparoscopic surgery. A total of 78 patients received chemotherapy, and of these 61 (78.2%) developed CIA. At last follow-up, 38.7% (24/62) patients developed IDA, and 79.5% (101/127) were anemic. Red blood cell (RBC) transfusions were most frequently prescribed (49.1%; median 4 units, IQR: 2-6.5), compared to oral (31.5%) or IV iron (16.3%) therapy.

Conclusions: There was a high proportion of IDA (58.7%) in our gastric cancer population despite inconsistent screening for ID. The incidence of anemia increased by 20% from the time of gastric cancer diagnosis to last follow-up. Approximately half of the patients received a RBC transfusion during their care. Our findings highlight the need for targeted therapy for ID to reduce RBC transfusion risk and to improve health-related quality of life. In response to our findings, we have implemented a quality improvement initiative that involves screening of iron status and provision of IV iron given limited oral absorption of iron in gastric cancer patients.

Legal entity responsible for the study: St. Michael’s Hospital

Funding: None

Disclosure: All authors have declared no conflicts of interest.

653P Is surgical resection beneficial in recurrent or metastatic gastric cancer?

Department of Hematology-Oncology, Ajou University School of Medicine, Suwon, Republic of Korea

Background: Although chemotherapy is currently established as a standard treatment in recurrent or metastatic gastric cancer, the role of palliative surgical resection is still controversial. We investigated the survival benefit of surgical resection in patients (pts) with recurrent or metastatic gastric cancer who received systemic chemotherapy.

Methods: A retrospective review was conducted on 696 pts who received palliative chemotherapy for recurrent (n = 307) or primary metastatic (n = 389) gastric cancer. Overall survival (OS) of pts who underwent surgical resection followed by chemotherapy was compared to that of pts who received chemotherapy alone.

Results: Among 138 pts (primary metastatic: 96, recurrent: 42) with surgical resection, gastrectomy, metastasectomy, and gastrectomy with metastasectomy were performed in 83 (primary metastatic: 81), 42, and 15 pts, respectively. Higher surgical resection rate was observed in pts with young age (<70) (p = 0.003), ECOG PS 0 or 1 (p = 0.010), primary metastatic (p = 0.0001), absence of liver metastasis (p = 0.003), and signet ring cell histology (p = 0.002). The median OS of pts who underwent surgical resection before chemotherapy was significantly longer than that of pts who received chemotherapy alone (19 vs. 9 months, p = 0.001). The OS benefit of surgical resection was consistent across subgroups in terms of baseline characteristics. In multivariate analysis, surgical resection was independently associated with favorable OS (hazard ratio=0.41, p < 0.0001) along with second-line chemotherapy (p < 0.0001), while...
ECOG PS 2 or 3 (p = 0.015), signet ring cell histology (p < 0.0001), and peritoneal metastases (p = 0.038) were independent prognostic factors of poor OS. In addition, the median OS of pts who underwent complete resection (n = 61) was significantly longer than that of pts who underwent incomplete resection (n = 77) (29 vs. 15 months, p = 0.005).

Conclusions: The present study suggests that judicious use of surgical resection before chemotherapy in recurrent or metastatic gastric cancer pts may result in favorable outcome, although large-scale phase III trials are essential to establish this treatment approach as a standard practice.

Legal entity responsible for the study: Ajou University School of Medicine

Funding: Samyang Biopharmaceuticals Corporation, Korea

Disclosure: All authors have declared no conflicts of interest.

**654P** Nomograms for pre- and post-operative prediction of long-term survival for patients of proximal gastric cancer: A large-scale, single-centre retrospective study

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Background: The prognostic prediction for long-term survival for patients of proximal gastric cancer has not been well established.

Methods: Between December 2006 and June 2013, we prospectively collected and retrospectively analyzed the medical records of 746 patients with upper-third gastric cancer (GC). The data were split 75/25, with one group used for model development and the other group used for validation testing. COX regression was used to identify preoperative and postoperative risk factors associated with OS.

Results: Among the 746 patients examined, the 1-, 3-, 5-year overall survival rate is respectively 89.4%, 66.1%. The preoperative T staging (T), preoperative N staging (N), ASA score, preoperative CA199, preoperative tumor size and the weight loss of 3-6 months were incorporated into the preoperative nomogram for overall survival (OS) prediction for the training set. In addition to these variables, LVI, postoperative tumor size, postoperative T stage, postoperative N stage, postoperative blood transfusion and postoperative complications were incorporated into the postoperative nomogram. All calibration curves for probability of OS fitted well. In the training cohort, the preoperative nomogram achieved a C-index of 0.751 [95% confidence interval (CI) 0.732-0.770] in predicting OS and accurately stratified patients into 4 prognostic subgroups (5-year OS rates: 86.4%, 73.0%, 43.72% and 20.9%, P < 0.001). The postoperative nomogram had a C-index of 0.759 in predicting OS and accurately stratified patients into 4 prognostic subgroups (5-year OS rates: 82.6%, 74.3%, 45.9% and 18.9%, P < 0.001).

Conclusions: The 2 nomograms showed accurate pre- and postoperative prediction for long-term survival for patients of proximal gastric cancer.

Legal entity responsible for the study: Changning Huang

Funding: None

Disclosure: All authors have declared no conflicts of interest.

**655P** Safety of neoadjuvant/adjuvant chemotherapy for gastroesophageal cancers: A single center experience

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Background: Neoadjuvant/adjuvant chemotherapy for gastroesophageal cancers leads to improvement in overall survival and is currently a standard practice. We performed a retrospective study at the Clatterbridge Cancer Centre to examine its safety and identify risk factors.

Methods: Patients with gastroesophageal cancers who received cisplatin/5-FU based neoadjuvant and/or adjuvant chemotherapy were identified from electronic records. We looked at the number of emergency hospital admissions and death events within 30 days from receiving chemotherapy. Information was collected from hospital registry data and medical notes. We also looked at performance status (PS) (0/I versus ≥ 2) and age (continuous variable) as potential factors for predicting the risk of death.

Results: We identified 1121 patients May 2002- Feb 2015. 73% were male; PS 0-1 in 91%, 2 in 6% and unknown in 3%; median age 64 years (16-81). 62% received cisplatin/5FU or cisplatin/captopribine (as in the OEO2 Trial) and 38% received epirubicin/cisplatin/captopribine (as in the MAGIC Trial). Mortality data was available for all patients whereas admission data was available for only 386 patients. There were 98 30-day admissions and those affected 83 patients (23%). The 3 most common causes for admissions were Gastrointestinal toxicities 43%, infection 13% and vascular events 10%. There were 31 30-day deaths (2.8%). There was no difference in mortality rates according to PS but older age was associated with a higher incidence of death (Mann-Whitney test: P = 0.002). The median age for patients who died within 30 days from chemotherapy was 69 years. The group of patients ≥ 70 years (26% of the study population) had an odds ratio of 2.37 for dying compared with patients < 70 years.

Conclusions: In our experience, mortality rate after neoadjuvant/adjuvant chemotherapy for gastroesophageal cancers was similar to that reported in landmark studies. In OEO2 3% of patients died before surgery and in MAGIC 1.6% died within 60 days from chemotherapy. PS did not seem to predict risk of death but this can be attributed to the good selection of patients as only 6% had a PS of 2. Patients > 70 years had a higher risk of death and this should be taken into consideration when assessing patients for chemotherapy.

Legal entity responsible for the study: Clinical Effectiveness Department, The Clatterbridge Cancer Centre NHS Foundation Trust

Funding: None

Disclosure: All authors have declared no conflicts of interest.

**656P** Peritoneal lavage CEA mRNA levels predict conversion gastrectomy outcomes after induction chemotherapy in gastric cancer patients with peritoneal metastasis

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Background: The outcome of gastric cancer patients with peritoneal metastasis remains poor. We treated these patients with intraperitoneal and intravenous administration of paclitaxel plus ortalizm/gemcitabine (ECOG), followed by gastrectomy in responders. However, it remains to be determined whether gastrectomy contributes significantly to the survival benefit in good responders. It is also unclear how and when gastrectomy should be performed. Therefore, reliable biomarkers are urgently needed to predict the outcome of gastrectomy. Herein, we evaluated the clinical significance of carcinoembryonic antigen (CEA) mRNA levels in peritoneal lavage as a biomarker for the indication of conversion gastrectomy.

Methods: The peritoneal lavage of 68 patients who received the above regimen as induction chemotherapy was repeatedly collected via intraperitoneal access ports. Gastrectomy was considered when improvement of peritoneal metastasis was confirmed by a second laparoscopic examination with negative peritoneal cytology. CEA and pheophorbilene deaminase (PBGD) mRNAs were chronologically quantified using the transcription reverse-transcription concerted reaction method. The CEA-mRNA Index (CmRI) was calculated as CEA mRNA/PGGD mRNA x 10,000.

Results: Thirty-nine patients received gastrectomy and 29 patients did not (median survival time (MST): 27.8 vs. 10.7 months, P < 0.001). In the gastrectomy-positive group, the outcome largely differed according the CmRI immediately prior to surgery. Patients (n = 20) who had a preoperative CmRI value of < 100 were associated with a significantly longer MST compared to patients (n = 19) who had a preoperative CmRI value of > 100 (41.8 vs. 20.8 months, P < 0.001). A preoperative CmRI value of > 100 was an independent predictor of survival for gastric cancer-positive patients in the multivariate analysis.

Conclusions: The CmRI reflects the response of peritoneal metastases to induction intraperitoneal chemotherapy. It may be a useful biomarker to determine gastrectomy in gastric cancer patients with peritoneal metastasis.

Legal entity responsible for the study: Hiroshi Yamauchi

Funding: Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science

Disclosure: All authors have declared no conflicts of interest.

**657P** Nutritional recovery after open and laparoscopic distal gastrectomy for early gastric cancer: A prospective multicenter comparative trial (ICCG21204)

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Background: Little information from prospective clinical trials is available on the influences of surgical approaches on postoperative body compositions and nutritional status. We designed a prospective non-randomized trial to compare postoperative...
chronological changes in body composition and nutritional status between laparoscopic and open distal gastrectomy for stage I gastric cancer (GC).

**Methods:** Body compositions and nutritional indicators in blood tests were measured at the baseline and at the 1st, 3rd, 6th and 12th postoperative months (POM). The primary endpoint was the decrease relative to the baseline in the body muscle mass at POM6.

**Results:** Ninety-six patients for the laparoscopic group and 52 for the open group were eligible for data analysis. No significant differences were found in any baseline demographic, body compositions and nutritional indicators between the groups. The changes of body muscle mass at POM6 were similar in both groups. Overall, no significant differences between the groups were observed in any of the body composition and nutritional indicators during the first year after surgery.

**Conclusions:** Postoperative body compositions and nutritional status was not affected by surgical approaches during the first 12 months after surgery in patients who underwent distal gastrectomy for stage I GC.

**Clinical trial identification:** UM11000015196

Legal entity responsible for the study: None

Funding: None

Disclosure: S. Ito: Personal fees from Olympus. Y. Kodera: Grants and personal fees from Johnson & Johnson, Coviden, and Otsuka Pharmaceutical Factory. All other authors have declared no conflicts of interest.

**Disclosure**: Although anthracycline-based triplets are one of the most widely used regimens for the treatment of advanced gastric cancer (AGC), the incremental benefit associated with the inclusion of anthracyclines in therapeutic combinations is unknown. The aim of this study is to evaluate the efficacy and tolerance of epirubicin triplets vs platinum-fluoropyrimidine doublets in a national AGC registry.

**Methods:** We recruited patients with AGC treated at 28 Spanish centers with polychemotherapeutic regimens (from 30% to 70% of patients received anthracycline-based triplets in 2016). The effect of anthracycline-based triplets was assessed by propensity score matching (PSM) and Cox proportional hazards (PH) regression.

**Results:** 1002 patients (doublets, n = 653, triplets with anthracyclines, n = 349) were included. In the multivariate Cox PH regression model, there was no significant increase in OS in favor of anthracycline-based triplets: HR 0.90 (95% CI, 0.78-1.05), p = 0.02035. After PSM, the sample contains 325 pairs with similar baseline characteristics. There was also no increase of OS with this method: 10.5 (95% CI, 9.7-12.3) vs. 9.9 (95% CI, 9.2-11.4) months, HR 0.91 (CI 95%, 0.76-1.083), (stratified log-rank test, p = 0.226), for doublets without anthracyclines vs anthracycline-based triplets. Objective responses were higher with triplets: 32.9% vs. 24.8% (p = 0.014) without significant differences in PFS: HR 0.95 (95% CI, 0.80-1.13) vs. 0.873. Triplets were associated with higher hematological toxicity, and increased toxicity-related admissions by 86%. The addition of epirubicin is viable, but 23.7% discontinued treatment because of adverse effects or patient decision.

**Conclusions:** Anthracycline triplets increased the antitumor effect (objective responses) of the treatment. However, they were not associated with an incremental benefit in PFS or OS and instead had a higher toxicity.

Legal entity responsible for the study: Paula Jimenez Fonseca

Funding: None

Disclosure: All authors have declared no conflicts of interest.
observed within 4 weeks of treatment the MT0 was not established. Mild-to-moderate gastrointestinal disorders (eg, nausea, vomiting) were the most common treatment-related adverse events (AEs); however, no clear dose dependency was observed. Neither of the 2 serious AEs (grade 2 oedema and grade 1 depressed urine output) (60 mg/m²) was considered treatment-related. No antibodies against IMAB362 were detected. Most patients (n = 12/15, 80%) showed progressive disease at Weeks 4–5 after a single IMAB362 IV infusion; however, 1 patient in the 600 mg/m² dose group had sta-
ble disease for ~2 months postinfusion. The linear, dose-proportional PK profile sup-
ports IMAB362 dosing at 300–600 mg/m² every 2 weeks.

Conclusions: Single-dose administration of IMAB362 was well tolerated up to 1000 mg/m² in this FIH dose-escalation study. These results encourage further clinical testing of IMAB362 in patients with CLDN18.2-positive GE.

Clinical trial identification: NCT00909025, May 18, 2009

Legal entity responsible for the study: Gyamied Pharmaceuticals AG, a company of Astellas Pharma, Inc.

Funding: Gyamied Pharmaceuticals AG, a company of Astellas Pharma, Inc.

Disclosure: U. Sahin: Stock option owner, ex-shareholder and co-founder of Gyamied Pharmaceuticals AG, founder, CEO, shareholder of Biontech Holding, several patents issued to this work that have been acquired by Astellas. M. Schuler: Work at University Hospital Zürich (USZ); B. Hauser: R0 resection was achieved in 63 of 94 patients (65%). Postoperative complications included anastomotic leakage in 3 patients and pancreatic fistula in 2 patients, which were cured conservatively. The median survival time (MST) of 94 patients with gastrectomy was 31.3 months (95% confidence interval [CI] 26.1–39.3 months) from the initiation of IP chemotherapy and 35.8 months (95% CI 28.3–40.1 months) from the diagnosis of gastric cancer. Relapse or progression was observed in 78 of 94 patients with a median time of 17.9 months (95% CI 13.8–24.2 months). The first site of recurrence or progression was the peritoneum in 61 patients and the other site in 28 patients (both in 11 patients). The MST of 64 patients without gastrectomy was 12.3 months (95% CI 10.1–14.9 months).

Conclusions: Gastrectomy after response to intraperitoneal and systemic chemotherapy is safe and may prolong the survival of P1 and CY1 gastric cancer patients.

Legal entity responsible for the study: The University of Tokyo

Funding: Japan Agency for Medical Research and Development

Disclosure: All authors have declared no conflicts of interest.

661P Bidirectional chemotherapy in gastric cancer (GC) with peritoneal carcinomatosis (PC) combining intravenous chemotherapy with pressurized intraperitoneal aerosol chemotherapy (PIPAC): Results of 103 procedures in 52 patients

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Background: Up to 43% of GC patients show synchronous PC at time of diagnosis and peritoneal relapse develops in 10–46% of cases after radical surgery. Systemic chemother-
apy shows low response rate (14–25%) and median survival of 8–10 months. Innovative therapeutic approaches are needed to improve survival.

Methods: Treatment protocol for untreated patients included initial staging laparosco-
py/laparotomy, 3-4 courses of systemic chemotherapy (XELOX) followed by Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) with low-dose Cisplatin and Doxorubicin every 4 weeks until progression of disease or death. Criteria of pro-
gression were 50% or more PCI increase or distant metastases. Patients with primary or recurrent GC with synchronous PC were selected. The lines of systemic chemotherapy, didn’t receive 4 XELOX courses before PIPAC. Primary endpoints were overall survival and pathologic response after peritoneal resection.

Results: 52 patients were included (15 men, 37 women, mean age 53.5 years), 38 pa-
tients had primary GC, 3 patients had peritoneal relapse after surgery (with or without adjuvant therapy). 19 patients had systemic chemotherapy before inclusion to the program. Mean PCI was 12.6 (min-max 3–34). Altogether, 103 PIPAC procedures were performed in the 52 patients. The main reason for not undergoing more than one PIPAC was PC progression (16). Pathological response was estimated in 30 pts under-
went PCI was most frequently

662P Gastrectomy after response to intraperitoneal and systemic chemotherapy for gastric cancer with peritoneal metastasis or positive peritoneal cytology

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Background: The prognosis of gastric cancer patients with peritoneal metastasis (P1) or positive peritoneal cytology (CY1) remains poor in spite of recent progress in sys-
temic chemotherapy. We developed several regimens combining intraperitoneal (IP) and systemic chemotherapy, and evaluated the safety and efficacy in clinical trials. Gastrectomy after response to combination chemotherapy is a promising option for P1 or CY1 gastric cancer. A retrospective study was performed to evaluate this multidisciplinary treatment strategy.

Methods: This study enrolled 158 primary P1 or CY1 gastric cancer patients treated with IP paclitaxel or doxetaxel with systemic chemotherapy at the University of Tokyo Hospital between 2005 and 2015. Gastrectomy was performed when peritoneal cy-
tology turned negative, and the disappearance or obvious shrinkage of peritoneal me-
tastasis was confirmed by laparoscopy. Combination chemotherapy was restarted after surgery and repeated with appropriate dose reduction.

Results: Ninety-one patients were chemo-naive, and 67 patients had received standard systemic chemotherapy at the previous hospitals before the initiation of IP chemother-
apy. Gastrectomy was performed in 94 (P1 85, P0CY1 9) of 158 (P1 147, P0CY1 11) pa-
tients after response to chemotherapy. R0 resection was achieved in 63 of 94 patients (65%). Postoperative complications included anastomotic leakage in 3 patients and pancreatic fistula in 2 patients, which were cured conservatively. The median survival time (MST) of 94 patients with gastrectomy was 31.3 months (95% confidence interval [CI] 26.1–39.3 months) from the initiation of IP chemotherapy and 35.8 months (95% CI 28.3–40.1 months) from the diagnosis of gastric cancer. Relapse or progression was observed in 78 of 94 patients with a median time of 17.9 months (95% CI 13.8–24.2 months). The first site of recurrence or progression was the peritoneum in 61 patients and the other site in 28 patients (both in 11 patients). The MST of 64 patients without gastrectomy was 12.3 months (95% CI 10.1–14.9 months).

Conclusions: Gastrectomy after response to intraperitoneal and systemic chemother-
apy is safe and may prolong the survival of P1 and CY1 gastric cancer patients.

Legal entity responsible for the study: The University of Tokyo

Funding: Japan Agency for Medical Research and Development

Disclosure: All authors have declared no conflicts of interest.

663P Change in the molecular profile of tumor tissues during treatment with trastuzumab, as analyzed by next-generation sequencing and immunohistochemistry: A multicenter prospective biomarker study on HER2-positive gastric cancer

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Background: Trastuzumab (Tmab) is an active molecular-targeted drug for HER2-
positive gastric cancer (GC) patients. However, continued use of Tmab beyond pro-
gression is not established in HER2-positive GC, unlike that of breast cancer. Therefore, we conducted this study to evaluate the resistance mechanism of anti-HER2 drugs in metastatic GC patients.

Methods: Metastatic HER2-positive GC patients treated with Tmab were registered prospectively, and tumor tissues were obtained by biopsy from primary lesions at the following points: (1) pre-treatment, (2) post-treatment, and (3) disease progression during chemotherapy with Tmab. Formalin-fixed paraffin-embedded tissue slides were prepared, and the expression of receptor tyrosine kinases (RTKs) such as EGFR, HER2, HER3, c-MET, FGFR2 and IGF-1R was evaluated by immunohistochemistry (IHC). Hot-spot mutations and copy number variations (CNVs) were analyzed by next-
geneneration sequencing (NGS) using Ion AmpliSeq Cancer Hotspot Panel v2.

Results: Twenty patients were enrolled and evaluated by IHC, and 15 of 20 patients were evaluated by NGS. One patient was excluded because HER2 status was revealed as negative after registration. HER2 expression (≥2+) by IHC have disappeared after treatment in 8 patients (42%). FGFR2 expression (≥2+) by IHC was most frequently
Phase 1 Study of IMAB362 with immunomodulation in patients with advanced gastric cancer


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Background: IMAB362, a monoclonal antibody to Claudin 18.2 (CLDN18.2), has demonstrated strong tumor cell killing activity via antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) in preclinical gastric cancer models. Safety/tolerability, pharmacodynamics (PD), and clinical response of IMAB362 in combination with zoledronic acid (ZA) and interleukin-2 (IL-2), which can also activate ADCC-mediated gamma/delta T cell effectors, was assessed in patients with advanced upper GI adenocarcinomas.

Methods: This open-label phase 1 exploratory study (NCT01617774) enrolled heavily pretreated patients (age 18–75 yrs) whose tumor cells had CLDN18.2 staining intensity either 2+/3+ in ≥ 40% of cells or any ≥ 1+ by IHC. Patients were enrolled into 1 of 4 treatment arms: Arm 1: IMAB362 + ZA; Arm 2: IMAB362 + ZA + 1 million IU (mIU) IL-2; Arm 3: IMAB362 + ZA + 3 mIU IL-2; Arm 4: IMAB362 alone. Patients received IMAB362 Q3W, 800 mg/m² on Cycle 1, Day 1 and 600 mg/m² on Day 1 of every subsequent cycle; IV ZA 4 mg, Day 1 of Cycles 1 and 3; subcutaneous IL-2, Days 1–3 of Cycles 1 and 3. Safety/tolerability of IMAB362, immune cell phenotyping by flow cytometry and IMAB362-induced ADCC in a cytotoxicity assay were primary endpoints; clinical response (per RECIST v1.1) was a secondary endpoint.

Results: Of the 29 enrolled patients, 28 received treatment (Arm 1, n = 7; Arm 2, n = 9; Arm 3, n = 7; Arm 4, n = 5); 21 were in the PD analyses, and 19 in response analyses. IMAB362 had a acceptable safety/tolerability unaltered by immunomodulation; grade 1–4 nausea and vomiting (both n = 15/28; 54%) were the most common adverse events. Expansion and activation of gamma/delta T cells and activation of NK cells were initiated by all treatment arms; however, these effects were more extensive in patients treated with IMAB362 + ZA/IL-2 (n = 10 [5 each in Arms 2 and 3]). A strong ADCC in response to IMAB362 was observed in most patients; however, ADCC kinetics over time and dependency on ZA/IL-2 were not conclusive. No patient achieved confirmed response; 11 (58%) had confirmed stable disease.

Conclusions: This study provided encouraging data on safety/tolerability and cytotoxicity of IMAB362 in combination with ZA/IL-2. Objective responses were not observed.

Clinical trial identification: NCT01617774, August 21, 2012

Legal entity responsible for the study: Ganymed Pharmaceuticals, A company of Astellas Pharma, Inc

Funding: Ganymed Pharmaceuticals, A company of Astellas Pharma, Inc

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Modified Glasgow prognostic score, prognostic nutritional index and ECOG score could be new prognostic factors for survival in metastatic gastric cancer


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Background: Metastatic gastric carcinoma (MGC) patients usually present with cachexia and sarcopenia. We aimed to analyze the prognostic values of the sarcopenia index (SI), cachexia index (CI) and inflammatory indexes (advanced lung cancer inflammation-angiogenesis index (ALI), modified Glasgow Prognostic Score (mGPS), prognostic index (PI), prognostic nutritional index [PNI] and neutrophil-to-lymphocyte ratio [NLR]) on MGC, at presentation.

Methods: A retrospective study was performed in 87 patients with MGC. SI, CI, PNI, ALI, mGPS and NLR was measured and calculated appropriately. Due to lack of studies from our country, SI cutoff value has been obtained by using both western (EGWISOP) and eastern (Harada Y, et al) sources separately. Statistical analysis has been done by SPSS.

Results: Median follow-up time was 9 months (range 1-64) and 78 patients died during follow-up. Fifty-nine patients were male (63%) and median age was 62 (23-88). According to univariate analysis these factors had significant negative impact on general survival (GS): increased leucocyte (p = 0.003) and neutrophil (p < 0.001), decreased lymphocyte count (p = 0.048), increased CRP (p < 0.01), and decreased serum albumin (p < 0.001), high mGPS (p = 0.001) and PI score (p < 0.001). PI score ≤ 3,41 (p < 0.001), NLR ≤ 3,41 (p < 0.001), ALI ≤ 5 (p < 0.001), SI (Harada Y, et al) ≤ 44,5 (p < 0.003), PI score ≤ 2 (p < 0.001), weight loss more than 10% during last 6 months (p = 0.002), BMI under 24 (p = 0.009). According to multivariable analysis mGPS (HR 2,494, 95% CI 1,25–4,94 p = 0,02), PNI (HR 4,2, 95% CI 1,73–10,1 p < 0.001) and ECOG score (HR 1,541, 95% CI 1,089–2,412, p = 0.004) were independent prognostic factors on GS. mGPS was found to be more valuable than other indexes for predicting mortality. The time consumed during these tests were: mGPS 10 sec, PNI 20 sec, PI 15 sec, NLR 15 sec, ALI 40 sec, CI 17 min, SI 15 min.

Conclusions: On our study, mGPS, PNI and ECOG score were independent indicators for shorter survival. mGPS and PNI, which can be calculated by using only CRP, albumin levels and complete blood counts, might be inexpensive, practical and beneficial in routine clinical practice.

Legal entity responsible for the study: Marmara University Pendik Treatment & Research Hospital, Medical Oncology Department

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Accuracy and prognostic significance of oncologists’ estimates and scenarios for survival time in a randomised Phase 2 trial of regorafenib in advanced gastric cancer


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Background: We have proposed that best, worst and typical scenarios for survival, based on simple multiples of an individual’s expected survival time (EST) estimated by their oncologist, are a useful way of formulating and explaining prognosis in advanced cancer. We aimed to determine the accuracy and prognostic significance of such estimates in a multicentre, randomised trial.

Methods: 68 oncologists estimated the EST at baseline for each of 152 participants in the INTEGRATE trial. We expected oncologists’ estimates of EST to be well calibrated.

Annals of Oncology
ERBB3 mutations in advanced gastric signet-ring cell carcinoma (SRCC) and the implications for targeted therapy

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Background: Studies have shown that ERBB3 mutations are associated with poor clinical prognosis by increasing the rate of metastasis and recurrence in many cancers. ERBB3 targeted therapeutics can be effective against ERBB3 mutant-driven tumors. ERBB signal pathway plays a very important role in the initiation and progression of gastric cancer, however the ERBB3 expression and mutation rate is relative low especially in gastric SRCC. Thus, ERBB3 might be a promising target for the treatment in SRCC patients. The aim of this study is to speculate the prognostic and targeted therapy value of ERBB3 in gastric SRCC by evaluating the mutation rate and type of ERBB3.

Methods: 92 patients with histological diagnosis of advanced gastric SRCC were retrospectively selected for this study. ERBB3 mutation was evaluated by next generation sequencing from formalin-fixed paraffin-embedded (FFPE) samples. ERBB3 expression was tested by immunohistochemistry. Correlations between ERBB3 expression and clinical pathologic characteristics and overall survival (OS) were performed.

Results: All of the 92 patients were diagnosed as local advanced or metastatic gastric SRCC (92.4% were stage III, 7.6% were stage IV). All the patients received 5-FU-based first-line chemotherapy. 14 out of all 92 patients were ERBB3 mutated SRCC, 12 out of all the 14 mutations were in the extracellular domain, 2 were in the transmembrane region. There was no correlation between ERBB3 mutation and sex (P = 0.367) or lymph node metastasis (P = 1.000). The median OS was 20.5 months (95% CI = 10.05 to 30.95 months) for patients with ERBB3 mutation, and 19.0 months (95% CI = 15.54 to 22.46 months) for patients without ERBB3 mutation (P = 0.567). There was no difference in OS according to HER2 positive or negative in ERBB3 mutated patients (14.8 months vs 20.5 month, P = 0.374).

Conclusions: Our study demonstrated 15.2% of gastric SRCC patients harboring ERBB3 mutation, providing a potential subgroups of gastric SRCC for targeted treatment on ERBB3 pathway. There are no difference of OS was observed, probably due to the relative small sample size and low ERBB3 positive rate in SRCC patients. Further investigation on ERBB3 is warranted to clarify mechanisms of ERBB pathway in SRCC.

Legal entity responsible for the study: The Comprehensive Cancer Centre of Drum Tower Hospital, Medical School of Nanjing University & Clinical Cancer Institute of Nanjing University, Nanjing 210008, China

Funding: None

Disclosure: All authors have declared no conflicts of interest.

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Legal entity responsible for the study: The Comprehensive Cancer Centre of Drum Tower Hospital, Medical School of Nanjing University & Clinical Cancer Institute of Nanjing University, Nanjing 210008, China

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Disclosure: All authors have declared no conflicts of interest.

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Estimating 12-weeks life expectancy in metastatic gastric cancer (mGC) patients (pts) candidates for second-line treatment: The ‘Gastric Life’ nomogram

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Background: The estimation of life expectancy of mGC pts in the second-line setting may be biased by the absence of objective prognostic tools to be used for enrollment in clinical trials and for decision making in the daily practice. The availability of evidence-based second-line treatment options highlights the need of nomograms/nomographic scores which may assist clinicians in refining pts’ clinical selection in the salvage setting. The aim of this study was to build a nomogram for predicting the individual 12-weeks overall survival (OS) of mGC pts starting a second-line treatment.

Methods: At 26 Italian Institutions, 320 mGC patients receiving second-line chemotherapy, ramucirumab or paclitaxel-ramucirumab were used as developing set. Putative prognostic variables (age, gender, ECOG PS, T stage, Lauren’s histotype, primary anatomic site, synchronous presentation, number and location of metastatic sites, DFS and response to first-line, LDH, neutrophil/lymphocyte ratio) were selected using a random forest model and included in a Cox multivariable model from which the nomogram was derived. The nomogram performance was evaluated by means of calibration plot and discriminatory ability (Harrell’s C index).

Results: Three variables were selected and included in the nomogram: ECOG PS (P < 0.0001), neutrophil/lymphocyte ratio (P < 0.0001) and peritoneal involvement (P < 0.0001). The model discriminatory ability index was 0.858. The internal calibration plot did not show significant differences between observed and predicted 12-weeks OS probabilities. External validation analysis is currently ongoing.

Conclusions: Our nomogram may be a useful tool to predict 12-weeks life expectancy in mGC pts candidates for second-line therapy. Based on 3 easy-to-collect variables, the ‘Gastric Life’ nomogram may improve second-line pts’ selection and assist researchers for the enrollment in clinical trials.

Legal entity responsible for the study: Filippo Pietrantonio

Funding: None

Disclosure: All authors have declared no conflicts of interest.
**Results:** To date, 19 pts (68% R1) have been followed for 2 1/2 yrs. Median CA19-9 was 15 (5, 240) U/ml at baseline. 8 SAEs in 5 pts have occurred; 4 related to gemcitabine (anemia, pulmonary infection and 2 fever); 3 related to TG01/GM-CSF (2 anaphylaxes and 1 hypersensitivity); and 1 possibly related to all products (dyspepsia). The allergic reactions only occurred after several cycles of gemcitabine and resolved without sequelae.

There were no treatment related deaths. TG01 induce an immune response in 17/19 patients by week 11, which demonstrate that TG01 vaccination activate TG01 specific T-cells. OS rate at 2yrs was 68.4% (95% CI 59.3-77.9) vs 39.3% (95% CI 30.4-48.2), p = 0.0002. OS rate at 2 1/2 yrs will be presented. Median OS was 33.1 months (95% CI 16.8, 40.1). Median DSS was 13.9 months (95% CI 5.4-21.0) months.

Conclusions: The regimen was generally well tolerated although some late, manageable allergic reactions were seen. OS and DSS was encouraging in view of published reports. TG01/GM-CSF generated early immune responses in 89% of patients with R0/R1 resected pancreatic cancer. 15 pts have been recruited in a modified dose cohort with 2 yrs data in 2Q 2018.

**Clinical trial identification:** NCT02261714.

**Legal entity responsible for the study:** Targovax ASA

**Funding:** Targovax ASA

**Disclosure:** T.J. Gjertsen, A.-S. Moller: Share options in Targovax ASA. A.K. Aknes: Stock options in Targovax ASA. D. Madsen: Stock options in Targovax ASA. Bayer, BMS. Consulting and advisory role: Celgene, Nucana, Bayer, BMS Research funding: Nucana, Bayer. All other authors have declared no conflicts of interest.

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A randomized, double-blind, multi-center phase III study evaluating paclitaxel with and without RAD001 in patients with gastric or esophagogastric junction cancer who have progressed after therapy with a fluoropyrimidine/platinum-containing regimen (RADPAC)


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**Background:** There is a need for effective treatments in the second- or further line setting in advanced gastric cancer, especially for new agents. In the current trial we evaluated paclitaxel with RAD001 (everolimus) in patients with gastric carcinoma who have progressed after therapy with a fluoropyrimidine/platinum-containing regimen.

**Methods:** This is a randomized, double-blind, multi-center phase III study. Patients with gastric carcinoma and adenocarcinoma of the esophagogastric junction (E/GJ) who have progressed after treatment with a fluoropyrimidine/platinum-containing regimen were randomly assigned to receive Paclitaxel (80 mg/m2) on day 1, 8 and 15 plus placebo (arm A) or RAD001 (10mg daily, arm B) d1-d28, repeated every 28 days as 2nd, 3rd or 4th line therapy. Primary end point was overall survival (OS), secondary end points were best overall response, disease control rate, progression free survival (PFS) and toxicity.

**Results:** 308 patients (median age: 62 years; median lines prior therapy: 2; 47.7% of patients had prior taxane therapy) were randomly assigned (Arm A, 150; Arm B, 158). In the intention to treat population, there was no significant difference in median PFS (placebo, 2.0 vs RAD001; 2.2 months, HR 0.9, p = 0.3) or median OS (placebo, 5.0 vs RAD001, 6.1 months, HR 0.93, p = 0.54). For patients with prior taxane use, RAD001 improved PFS (placebo 1.8 vs RAD001, 2.7 months, HR 0.69, p = 0.03) and OS (placebo 5.9 vs RAD001, 5.8 months, HR 0.75, p = 0.07). Combination of paclitaxel and RAD001 was tolerable, but the RAD001 arm was associated with significantly more grade 3-5 mucositis (13.3% vs. 0.7%; p = 0.001).

**Conclusion:** The addition of RAD001 to paclitaxel/RAD001 did not improve outcomes in pretreated metastatic gastric/E/GJ cancer. Of note, activity was seen in the taxane pretreated group. Additional biomarker studies are planned to look for subgroups that may have a benefit.

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**Interim safety and clinical activity of nivolumab (Nivo) in combination with s1-capetibin plus oxaplatin in patients (pts) with previously untreated unresectable advanced or recurrent gastric/ gastroesophageal junction (G/EJ) cancer: part 1 study of ATTRACTION-04 (ONO-4538-37) **


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**Background:** Nivo monotherapy demonstrated its efficacy with manageable safety for G/EJ cancer refractory or intolerant to standard chemotherapy in the pooled analysis (ATTRACTION-02 (ONO-4538-12): ASCO-GI 2017, Kang YK et al. J Clin Oncol. 2017; 35 (suppl 4S abstract 2)). This randomized phase 2/3 trial is to evaluate the efficacy and safety of Nivo in combination with 1st line chemotherapy in unresectable advanced or recurrent G/EJ cancer (NCT02747696).

**Methods:** This trial includes previously untreated pts aged ≥ 20 years with ECOG PS 0-1 and had measurable, unresectable advanced or recurrent HER2 (-) G/EJ cancer. It consists of 2 parts. Part 1 is a randomized, open-label trial to evaluate the feasibility of Nivo (360 mg, Q3W) in combination with oxaplatin (130 mg/m2, Q3W) plus either S1 (40 mg/m2 twice daily, daily 1-14, SOX) or capetibin (1000 mg/m2 twice daily, daily 1-14, CapeOX) in terms of activity and safety. Part 2 is a randomized, double-blind, placebo-controlled trial comparing Nivo to placebo in combination with SOX/CapeOX in terms of overall survival and progression free survival (PFS).

**Results:** A total of 40 pts were included into part I, 21 pts were randomized to Nivo-SOX and 19 to Nivo-CapeOX. The median age was 62.3 years, 27 pts (67.5%) were male, 20 pts (50.0%) had ECOG PS 1. Median duration of treatment was 7.03 months (range 0.3-9.9) as of 24 Feb 2017. Both treatments were well tolerated. Grade 3-4 treatment-related adverse events (AEs) were reported 23 pts (57.5%). No Nivo-related AEs leading to discontinuation were reported. Overall response rate was 68.4% (26/38, CR10, PR16) and disease control rate was 86.8%. Median PFS was not reached. 18 pts (46.2%) remain on treatment at the data cut off. There were no significant differences in activity and safety between the 2 treatments.
Background: This is a single-arm study (NCT01956149) to determine prolonged (>~4 months) disease control rate with cabazitaxel administered in second- (or later) setting for patients with advanced or metastatic adenocarcinoma of the esophageogastic junction (EGJ) and stomach.

Methods: 65 patients with advanced EGJ and stomach cancer were treated with 24mg/m² Cabazitaxel every 3 weeks for a maximum of 6 cycles. Main objective of the study was a prolonged Disease Control Rate (pDCR: CR, PR or SD lasting at least 4 months). Secondary Outcome Measures were overall survival (OS), progression-free survival (PFS), response rate by subgroup (vs without previous treatment with a taxane) and toxicity. Response rates were measured at the end of every 6 weeks during therapy and during follow-up (up to 12 months).

Results: 65 patients (median age: 65, range 31-86 years) were assigned to treatment. Median duration of prior therapies was 2.89 months. The patients received a median of 2 cycles of cabazitaxel. Efficacy results are for the per protocol (PP) population. pDCR was 22.7% (95%CI 15.0%-33.5%). pDCR was 20.9% in 2nd line patients (95%CI 6.8%-40.9%) and 30.0% (95%CI 6.7%-63.2%) in all lines in patients without prior taxane use. Response rate was 5.5% (95%CI 1.1%-15.1%) in total PP and 20.0% in the population without prior taxane use. Median OS was 4.6 months (7.4 months without prior taxane use vs 3.8 months with prior taxane use). Median PFS was 1.38 months (95%CI 1.28-1.87) with and 2.01 months (95%CI 0.20-4.47) without prior taxane use. Most common grade 3/4 toxicities were neutropenia in 13% of the patients, pain (12%), leucopenia (10%), anaemia (10%), fatigue (10%) and nausea (10%).

Conclusions: Cabazitaxel is active in heavily pretreated patients with metastatic and advanced esophageogastic junction and gastric adenocarcinoma. Toxicity is moderate. Patients without prior taxane use derived more benefit from Cabazitaxel.

Clinical trial identification: NCT01956149

Legal entity responsible for the study: Institute of Clinical Cancer Research Funding: Sanofi

Disclosure: All authors have declared no conflicts of interest.
Results: MSI status was determined in 25 pts; 7 (28%) were MSI-H, and 18 (72%) were non–MSI-H. ORR per INV was 29% in MSI-H pts, 11% in non–MSI-H pts, and 9% in pts with unknown MSI (MSI-U). DCR was 71%, 28%, and 26%, respectively. Of the 7 responders, 3 were PD-L1+ (5% tumor expression) and 2 were PD-L1− (MSI-U, n = 2; non–MSI-H, n = 1). In the non–MSI-H pts, safety for the full EG cohort was previously reported (Janjigian YY, et al. ASCO 2016 [abstract 4010]).

Conclusions: In this subgroup analysis, 7 pts (28%) were MSI-H, representing a biologically unique subset of EG tumors. NIVI monoetherapy led to survival benefit and responses in both MSI-H and non–MSI-H pts.

Clinical trial identification: CA209032 Revised Protocol 06, dated 18-Nov-2015

Legal entity responsible for the study: Bristol-Myers Squibb

Funding: Bristol-Myers Squibb

Disclosure: P.A. Ott: Grants, personal fees and non-financial support from BMS during the conduct of the study; grants/personal fees from BMS, Merck and Celldex, Amgen, Alexion, Pfizer, Cytorix, AZ/Immunomedics and ArmoBio outside the submitted work. P.A. Ascierto: Grants and personal fees from BMS, Roche-Genentech, MSD, Array, Novartis, Amgen,Merck Serono, and Pierre Fabre outside the submitted work. P. Sharma: Consultant/Advisor for BMS, GSK, AstraZeneca, Amgen, Constellation, Jounce, Novartis, Neo, Eveso, EMD Sereno, and Astellas, during the conduct of the study; Stock with Jounce, Kate Pharma, Eveso, Constellation, and Neon. H. Taniguchi: Patent owned by Pfizer outside the submitted work. P. Bonomi: Honoraria from Pfizer, BMS, Onyx Pharma, Novartis and MSD; research grant from Novartis, outside the submitted work; Stock Ownership: TilBc Therapeutics K. Pethela: Personal fees from BMS, Roche, Onyx Pharma, and MSD; outside the submitted work; Stock Holder: Faron Pharmaceuticals D. Jager: Consulting/advisory role for Roche, BMS and Bayer T.R. Evans: Personal fees/non-financial support from BMS, Eisai, Clovis Oncology, Thai Therapeutics, Basalsa, Bayer, Celgene, GSK, Otsuka, Roche-Genentech, TC Biopharm, Immunova, Basalsa, e Therapeutics, Immunocore, Vertex, Verastem, Dainich and Merck F. de Braud: Advisory boards and/or travel support from Amgen, Celgene, Novartis, Roche, BMS, MSD J. Chau: Advisory Board: Sanofi Oncology, Eli-Lilly, Bristol Meyers Squibb, MSD, BAYER; Roche, Free Five Therapeutics; Research Funding: Jansen-Cilag, Sanofi Oncology, Merck-Serono, Novartis; Honorarium: Taisho, Pfizer, Amgen, Eli-Lilly, Gilead Science J.C. Bendell: Payment to institution from the study sponsor for performing the study M. Tschaika, C.T. Harbison: Employee of BMS E. Calvo: Personal Fees/Non-financial support: Astellas Pharma, GSK, Lilly/ImClone, Nanobiotix, Novartis, Pfizer, Roche/ Genentech, PixOxus Thier, Abbvie, Boehringer Ingelheim, BMS, Eisai, Jansen, Merck, Millenium, Nektar, OncoMed, PharmaMar, Puma Biotech, Sanofi, Spectrum Pharm. All other authors have declared no conflicts of interest.

676P

Involvement of the immunoregulator MZB1 in progression of gastric cancer


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Background: The initiation and progression of gastric cancer are associated with inappropriate immune responses caused by chronic inflammation of the gastric mucosa. Methods: To identify immunoregulatory molecules involved in gastric cancer progression, transcriptome analysis was conducted using tissue samples from patients with metastatic gastric cancer. Gastric cancer cells lines and 200 pairs (cancerous and non-cancerous) of gastric tissue samples from patients with gastric cancer were analyzed for gene expression, amplification, DNA hypermethylation and functions of the candidate molecule. Results: The transcriptome analysis revealed that marginal zone B and B1 cell specific protein (MZB1) was expressed at significantly decreased levels in primary gastric cancer tissues when compared with the corresponding normal gastric mucosa. PCR array analysis exploring genes expressed cooperatively with MZB1 revealed that differential expression of MZB1 mRNA in gastric cancer cell lines correlated positively with the levels of the mRNAs encoding estrogen receptor 1 and desmoylating isopeptidase 1. Hypomethylation of the MZB1 promoter was frequent in cell lines with decreased levels of MZB1 mRNA. siRNA-mediated knockdown of MZB1 significantly increased proliferation, invasion and migration of gastric cancer cell lines. Low MZB1 expression was an independent prognostic factor for recurrence after curative gastrectomy and was associated significantly with increased haematogenous recurrence.

Conclusions: The immunoregulator MZB1 acts as a suppressor and serves as a predictor for recurrence after curative resection in gastric cancer.

Legal entity responsible for the study: Mitsuro Kanda

Funding: None

Disclosure: All authors have declared no conflicts of interest.

676P

PD-L1 immunohistochemistry (IHC) by three different assays and molecular profiling in tissue microarray (TMA) of gastric cancer


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Background: Recent genomic and molecular characterization of gastric adenocarcinoma (GAC), such as Cancer Genome Atlas (TCGA), have shed light on the PD-L1 positivity and four different subtypes. Several PD-L1 IHC assays of scoring-criteria are developed in parallel. This study aimed to evaluate PD-L1 staining patterns and molecular profiling by TMA in gastric tumor blocks.

Methods: In total, 331 consecutive patients (pts) with GAC underwent curative surgery at Aichi Cancer Center Hospital between Jan 2009 and Dec 2010. Pts with no systemic chemotherapy before surgery and sufficient tumor content on the formalin-fixed and paraffin-embedded (FFPE) slides were eligible. EBV-encoded RNA in situ hybridization, IHC for deficient mismatch repair proteins (dMMR, MLH1/MSH2/MSH6/ PMS2), HER2 and PD-L1 (22C3, 28-8, E1L3), and HER2 DISH were evaluated in TMA. Four cores of tumor tissue were punched out from individual FFPE tumor blocks and arranged in a new TMA block. PD-L1 tumor positivity was categorized to ≥1% (MSI-U, ≥25%/≥50% tumor cell membrane staining, Disease free survival (DFS) and overall survival (OS) were estimated by the Kaplan-Meier method.

Results: Among the cases, 226 pts were included in this study, excluding pts with prior chemotherapy (n = 26) and insufficient tumor samples (n = 79). Patient characteristics were as follows: male/female, 162/64, pStage (AJCC 7th ed.) IV/II/III/IV, 108/59/58/29; EBV +/−/+/−, 132/213; proficient MMR/dMMR, 197/29, HER2 +/−/+, 24/202; and PD-L1 ≥1%/≥25%/≥50% (22C3 vs. 28-8 vs. E1L3), 11/4/2 vs. 7/6/6 vs. 12/10/8. Among 22C3, 28-8, and E1L3 assays, 94–97% of the pairs were concordant. PD-L1 positivity by all three assays was associated with EBV + (p < 0.05), whereas only 28-8 staining positivity was correlated with dMMR (p = 0.04). EBV +, dMMR, and HER2 + were mutual except three pts who had both dMMR and HER2 +. There was no significant difference in DFS and OS among EBV, MMR, HER2 and PD-L1 status.

Conclusions: The three tested PD-L1 assays did not show comparable staining patterns in all cases. Studies that correlate not only PD-L1 staining patterns but also EBV +/dMMR/HER2 + and response to immunotherapy are required to evaluate.

Legal entity responsible for the study: None

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Table: 674P

Table: 674P ORR and BOR per INV according to MSI status

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<thead>
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<th>Non–MSI-H n = 18</th>
<th>MSI-U n = 34</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, (%)</td>
<td>2 (29)</td>
<td>7 (41)</td>
</tr>
<tr>
<td>BOR, (%)</td>
<td>2 (11)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>CR</td>
<td>1 (14)</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>1 (14)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>SD</td>
<td>3 (43)</td>
<td>3 (17)</td>
</tr>
<tr>
<td>PD</td>
<td>2 (29)</td>
<td>11 (61)</td>
</tr>
<tr>
<td>Not evaluable</td>
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<td>2 (11)</td>
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</table>

Table: 676P

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<tr>
<th>EBV+</th>
<th>EBV−</th>
<th>P</th>
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<th>dMMR</th>
<th>MMR</th>
<th>HER2</th>
<th>HER2+</th>
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</thead>
<tbody>
<tr>
<td>N = 13N = 213</td>
<td>N = 197N = 29</td>
<td>N = 24N = 202</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E1L3 +</td>
<td>−3</td>
<td>9</td>
<td>204</td>
<td>0.02</td>
<td>8191</td>
<td>4.25</td>
<td>0.0602</td>
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</tr>
<tr>
<td>28-8 +</td>
<td>−3</td>
<td>10</td>
<td>209</td>
<td>&lt;0.014</td>
<td>193</td>
<td>3.26</td>
<td>0.0404</td>
<td>7</td>
</tr>
<tr>
<td>22C3+</td>
<td>−3</td>
<td>10</td>
<td>205</td>
<td>0.02</td>
<td>8188</td>
<td>3.26</td>
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</tr>
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</table>
Background: The choice of first-line chemotherapy in advanced HER2-negative gastric cancer (AGC) is based on the center's preferences and adverse effects profile. There is neither a standard accepted regimen nor predictive factors for drug response in clinical practice other than HER2 status. The objective is to evaluate whether Lauren's classification influences the efficacy of different chemotherapies and the survival of patients.

Methods: The data come from a national registry of AGC in which 31 Spanish centers participated. Eligibility criteria include the diagnosis of a primary gastric adenocarcinoma, HER2 negativity, and the use of two or three drug chemotherapy combinations. We used Cox proportional hazards (PH) regression with treatment-by-histology interaction tests to estimate the therapeutic effects.

Results: The registry contains 1215 HER2-negative tumors that could be analyzed for treatment efficacy. Tumor subtypes based on Lauren's classification predicted different treatment responses and corresponded differently to chemotherapy. Future clinical trials should stratify patients according to Lauren's classification.

Conclusion: In this registry, tumor subtypes based on Lauren's classification predicted different treatment responses and corresponded differently to chemotherapy. Future clinical trials should stratify patients according to Lauren's classification.
680P Phase II study of modified docetaxel, cisplatin and s-1 (mDCS) combination chemotherapy in patients with unresectable metastatic gastric cancer


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Background: We have previously conducted phase II studies to evaluate the effect of adding docetaxel to base treatment with S-1 plus cisplatin (DCS) to further improve the therapeutic response; both a very high response rate (67.1%) and a promising median survival time (687 days) in patients with unresectable advanced gastric cancer were noted (Y. Sato et al. Cancer Chemother Pharmacol. 2009); however, it also showed a high incidence of grade 3/4 toxicity. With the aim of reducing toxicities, we conducted a phase II study of modified DCS (mDCS), using a reduced dose of docetaxel, and evaluated the clinical efficacy and adverse events of this regimen.

Methods: Patients with unresectable gastric cancer received chemotherapy with S-1 (40 mg/m² b.i.d) on days 1–14, and docetaxel (50 mg/m²) plus cisplatin (60 mg/m²) on day 8 every 3 weeks. The primary endpoint was the response rate (RR). Overall (OS) and progression-free survival (PFS), and toxicities were also evaluated.

Results: Forty-nine patients were enrolled from November 2011 to April 2014, and 47 were eligible. The overall RR was 78.8%, including two cases of a complete response (4.3%), and 35 cases of a partial response (74.5%). Ten cases had stable disease (21.3%), but none showed progressive disease. Of the 47 cases, 16 cases (34.0%) underwent curative conversion surgery. The median PFS was 350 days (95% CI, 238–406 days) and median OS was 561 days (95% CI, 401–783 days). Grade 3/4 neutropenia developed in 76.6%, and febrile neutropenia in 31.9%, of patients. Non-hematological grade 3/4 adverse events were anorexia (23.4%), nausea (4.3%), and diarrhea (8.5%).

Conclusions: mDCS therapy showed high clinical efficacy and fewer toxicities, but careful management of these is still essential.

Clinical trial identification: UMIN00002361

Legal entity responsible for the study: Tokushima-Hokkaido Cancer therapy clinical trial group, Tetsuji Takayama

Disclosure: All authors have declared no conflicts of interest.

681P Clinical impact of programmed death ligand-1 and -2 expression after platinum based chemotherapy in metastatic gastric cancer

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Background: The effect of chemotherapy on programmed death ligand-1 (PD-L1) and PD-L2 expression is not well known. Therefore we aimed to investigate the effect of chemotherapy to PD-L1/2 expression in metastatic gastric cancer (mGC).

Methods: We evaluated the PD-L1 and 2 expression of 63 patients with paired tumor tissue before and after 5 to 4 cycles of palliative first line platinum-based chemotherapy. PD-L1/2 expression was detected by immunohistochemistry (IHC) method in paired tumor specimens.

Results: There were no significant differences in PD-L1 and PD-L2 expression across various clinicopathological parameters. The detection of PD-L1 on tumor cells decreased from 58% to 38% after chemotherapy (p = 0.028), but not with PD-L2 (from 43% to 36%). Among patients with objective response (CR and PR), PD-L1 expression decreased with statistical significance (p = 0.031), but not among patients with SD and PD (p = 0.275). In univariate and multivariate analysis, patients with positive PD-L1 at the pre-chemotherapy showed better progression free survival (PFS, hazard ratio [HR] = 0.42, p = 0.014). In patients with positive PD-L1 showed decreased PFS (HR = 1.97, p = 0.023). And pre-chemotherapy PD-L1 statuses didn’t have any correlation with OS difference, however, post-chemotherapy negative PD-L1 prolonged OS (HR = 1.92, p = 0.046). PD-L2 statuses had no difference of PFS and OS before and after chemotherapy. Univariate and Multivariate analysis showed that negative to positive change and positive to negative change of PD-L1 expression was associated with poorer PFS (HR = 0.030, p = 0.03) and better PFS (HR = 0.02, p = 0.024), respectively.

Conclusions: Our data suggests that chemotherapy may have an effect on the status of PD-L1/2 expression. PD-L1/2 expression may change during chemotherapy, so we suggest monitoring the pattern of change through serial tumor samples to reflect the correct status of PD-L1 expression.

Legal entity responsible for the study: In-Ho Kim

Funding: None

Disclosure: All authors have declared no conflicts of interest.

682P Clinical practice observation of trastuzumab (TRA) in patients (pts) with HER2-positive metastatic adenocarcinoma of the stomach (mGC) or the gastro-oesophageal junction (mGEJ) treated with anti-HER2 therapy in HERMES


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Background: HER2-pos metastatic cancer of GEJ or stomach are indications with a high medical need. TRA plus standard chemotherapy (CT) has been approved as 1L therapy in HER2-pos mGC or mGEJ-c pts according to ToGA-study. HERMES (NCT01220994) was designed to collect data on clinical routine practice in 171 specialist centers in Germany.

Methods: Between January 2010 and July 2016, 634 pts were identified. 364 pts matched criteria for TRA-therapy and were treated accordingly (population of the present analysis). Another 39 pts did not match criteria for HER2-positivity with TRA-therapy and will be evaluated separately. Main parameters of interest were overall response rate (ORR), progression free survival (PFS), safety and overall survival (OS); QoL and patient reported outcomes will be presented later.

Results: Mean age was 65 years, 75% were male, and 51% had mGEJ-C. TRA was given at an average dose of 5.37 mg/kg. Mean treatment duration for TRA was 7 months (range, 0.5 to 9.3). 81 pts (17%) received TRA-therapy for more than 1 year. CT regimen frequently used were cisplatin/5-FU (21%), oxaliplatin/5-FU/docetaxel (10%), and cis-platin/capecitabine (8%). ORR was 43% (95%CI 0.38;0.49), median PFS was 7 mos (6.3;7.6), and median OS was 10 mos (8.6;11.1). Most frequent related AEs (reported in > 5% of pts) were diarrhea in 29 (8%), nausea in 24 (6.6%) and fatigue in 22 cases (6%). TRA-ref cardiac AEs occurred in 21 pts (6%).

Conclusions: To our knowledge this is the largest prospective observational trial on TRA in the daily clinical routine care of metastatic GC/GEJ-C. Chemotherapy backbones were diverse. The outcome was similar to ToGA, taking into account the unselected patient population.

Clinical trial identification: NCT01220994

Legal entity responsible for the study: Roche Pharma AG
683P Intratumoral PD-L1 expression is associated with worse survival of patients with Epstein-Barr virus-associated gastric cancer


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Background: This study investigated the clinical relevance and prognostic significance of the overall expression of programmed cell death protein ligand-1 (PD-L1) and programmed cell death protein ligand-2 (PD-L2) in patients with Epstein-Barr virus-associated gastric cancer (EBVaGC).

Methods: After reviewing 1318 consecutive cases of surgically resected or endoscopic submucosal disected gastric cancers, the expression status of PD-L1 and PD-L2 in 120 patients with EBVaGC identified by EBV-encoded RNA in situ hybridization was retrospectively analyzed using immunohistochemistry (IHC). For each IHC marker, positivity was separately in intratumoral epithelial tumor cells (iTu-) and immune cells in the tumor stroma area (str-).

Results: Among 116 eligible patients, 57 (49.1%) and 66 patients (56.9%) were determined as iTu-PD-L1-positive and str-PD-L1-positive, respectively, with 23 (21.6%) and 45 patients (38.8%) were determined as iTu-PD-L2-positive and str-PD-L2-positive, respectively. iTu-PD-L1 positivity was found to be significantly associated with lymph node (LN) metastasis (p<0.01) and a poor disease-free survival (DFS) (p<0.003), yet not overall survival (p=0.482). Meanwhile, str-PD-L1 positivity correlated with the density of iTu- and str-tumor-infiltrating lymphocytes (TILs) (p=0.003; P=0.004, respectively), yet not the patient outcomes. In contrast, str-PD-L2 positivity was associated with a lower T category (p=0.003), absence of LN metastasis (p=0.002) PD-L2 in iTu- and str-TILs (p=0.001; p=0.001, respectively). iTu- and str-PD-L2 positivity showed a trend towards an improved DFS, although not significant (p=0.06; p=0.073, respectively). In a multivariate analysis, iTu-PD-L1 positivity was independently associated with a poor DFS (p=0.006; Hazard ratio =12.085).

Conclusions: iTu-PD-L1 expression can be used to predict a poor outcome in patients with EBVaGC, and can represent a rational approach for PD-L1/PD-L2 pathway targeted immunotherapy.

Legal entity responsible for the study: N/A

Funding: None

Disclosure: All authors have declared no conflicts of interest.

684P Targeting c-met and DNA double-strand break (DSB) repair pathways for BRCA-mutated gastric carcinomas

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Background: In the present study, we underline the importance of combining c-Met Inhibitor (Inh.) and DSBR repair Inhibitor (PARP Inh.) with the goal of accomplishing a synergistic therapeutic strategy in BRCA-mutated gastric carcinomas.

Methods: Firstly, to verify whether c-Met affects tumor response to PARP Inh., AGS (low c-Met expression) and Hs746T (high c-Met expression) cell lines, were subjected to knockdown c-Met expression, in the presence of PARP Inh. (NU1025). Subsequently, we examined the effect of BRCA1/2 and c-Met. We knocked down BRCA1/2 expression in AGS and Hs746T cells and treated them with PARP Inh. Next, we examined the effect of combining c-Met Inh. (SU11274) and PARP Inh. (NU1025), measured by MTT, clonogenic cell survival and Annexin, assays. We also evaluated the effect of combining PARP Inh. and c-Met Inh. in AGS/Hs746T xenograft tumor models. AGS/Hs746T -pcDNA3 and AGS/Hs746T -siRcra were injected into SCID mice. Tumor sizes were measured every 3 days. DNA damage was assessed by γ-H2AX staining.

Results: Silence of Met expression promoted Hs746T cells more sensitive to PARP Inh. to similar levels as the AGS cells, as indicated by decreased cell viability. Silence of BRCA1/2 expression sensitized only AGS cells, signifying that increased expression of c-Met renders cells resistant to PARP Inh. in the context of inactivating BRCA1/2. Combining c-Met Inh. and PARP Inh. suppressed cell growth and clonogenicity and enhanced apoptosis in both AGS and Hs746T cells. The dual inhibition was demonstrated to be even more successful when cells were knockdown for BRCA1/2. Also, co-inhibition treatment substantially reduced tumor growth to AGS/Hs746T -pcDNA3 and more even effectively to AGSH/Hs746T -siBRCA1/2 xenograft models, compared to either Inh. alone. DNA damage was higher in AGS/Hs746T -siBRCA1/2 compared to AGS/Hs746T -pcDNA3 xenograft models.

Conclusions: BRCA deficiency renders gastric tumor cells sensitive to PARP inhibition. In addition, treatment with c-Met Inh. enhanced Hs746T sensitivity to the PARP Inh. Our data demonstrate that dual Met/PARP inhibition is synergistic providing an effective therapeutic strategy in BRCA-mutated gastric carcinomas.

Legal entity responsible for the study: M.V. Karamouz

Funding: None

Disclosure: All authors have declared no conflicts of interest.

685P Clinical efficacy observation for endostar combined with chemotherapy treating gastric cancer peritoneal carcinomatosis

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Background: The peritoneal carcinomatosis of gastric cancer is a current therapeutic difficulty and the related clinical data are still limited so far. In this study, we evaluated efficacy and safety of the recombinant human endostatin (Endostar) characterized by broad-spectrum anti-angiogenesis combined with chemotherapy on gastric cancer peritoneal carcinomatosis.

Methods: From Jan. 2014 to Dec. 2016, 33 advanced stage gastric cancer patients associated with peritoneal carcinomatosis were enrolled. Their pathological information, imaging as well as therapy information were retrospectively analyzed. Twenty-one patients only received systemic chemotherapy as control group, and twelve patients received Endostar combined with chemotherapy as combination therapy group. All the 33 patients were evaluated on phase-efficacy and followed-up to record survival time. The tumor size to progression (TTP), overall survival (OS), Objective Response Rate (ORR), disease control rate (DCR) and therapy-related adverse reactions were evaluated to confirm effect of Endostar therapy.

Results: All the patients were evaluable. The evaluation on efficacy indicated that Endostar combined with chemotherapy increased ORR (41.6% vs. 23.8%) and DCR (83.3% vs. 61.9%) compared with control group, although there was no statistical difference between them. The survival analysis indicated that Endostar combined with chemotherapy effectively extended time to disease progression (4.60 ± 0.32 months vs. 3.50 ± 0.34 months, P = 0.03) and the median OS (15.80 ± 3.4 months vs. 9.80 ± 0.7 months, P = 0.03) compared with single chemotherapy. Furthermore, the evaluation on adverse reactions indicated that combination therapy did not have more adverse reactions.

Conclusions: The recombinant endostatin with broad-spectrum anti-angiogenesis could effectively control the development of peritoneal carcinomatosis disease and extend survival with high safety and tolerance. However, further prospective study needs to be performed to confirm the clinical application value.

Clinical trial identification: This retrospective study was approved by hospital ethical committee and all informed consent were obtained.

Legal entity responsible for the study: This study was approved by hospital ethical committee and all informed consent were obtained.

Funding: None

Disclosure: All authors have declared no conflicts of interest.

686P Modified epirubicin and oxaliplatin plus capcitabine (EOX) Regimen as second-line therapy after failure of modified docetaxel and cisplatin plus fluorouracil (DCF) regimen in advanced gastric cancer

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Background: In advanced gastric cancer, we aimed to evaluate the effectiveness of mEOX regimen as second line therapy after failure of mDCF regimen.

Methods: In between 2009 and 2016, the patients who were progressed after mDCF (docetaxel 60 mg/m2 on day 1, cisplatin 60 mg/m2 on day 5 and 3 days) and received mEOX (epirubicin 50 mg/m2 on day 1, oxaliplatin 85 mg/m2/m2 day for 3 days) were included. Efficacy of this regimen was calculated as the response rate (RR), progression-free survival (PFS) and overall survival (OS). A total of 15 patients were included. Median follow-up time was 10 months at the end of follow-up. The proportion of patients with tumor response was calculated using the response evaluation criteria in solid tumors (RECIST).

Results: The RR was 40% (6/15). Median PFS and OS were 3.4 months and 6.8 months, respectively. The most common grade 3 and 4 adverse events were neutropenia, diarrhea, fatigue, thrombocytopenia, and anemia, which were managed with dose modifications. The toxicities grade 3 and 4 were found in 33% and 20% of the patients, respectively.

Conclusions: The mEOX regimen is well tolerated and effective in patients with advanced gastric cancer who progressed after mDCF regimen.

Legal entity responsible for the study: The study was approved by the institutional review board.

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Phase II clinical trial of second-line weekly paclitaxel plus trastuzumab for patients with HER2-positive metastatic gastric cancer

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Background: Combination therapy with fluorouracil, platinum, and trastuzumab (Tmab) has been established as the first-line chemotherapy for HER2-positive gastric cancer, but there is no established therapy in the second-line setting. This study aimed to evaluate the efficacy and safety of weekly paclitaxel plus Tmab as second-line chemotherapy for HER2-positive gastric cancer patients.

Methods: Eligible patients were ≥ 20 years old, histologically confirmed gastric adenocarcinoma with HER2-positive (IHC3+ or IHC2+ and FISH or ISH+) patients, pretreated with chemotherapy (not excepted Tmab), ECOG PS of 0 or 1, and adequate organ function. Eligible patients received weekly paclitaxel plus Tmab (paclitaxel: 80 mg/m2 IV day 1, 8, 15, repeated every 4 weeks, Tmab: 8mg/kg IV every 7 days, if grade ≤ 1 hand-foot-syndrome). All therapy was administered until disease progression. The primary endpoint was response rate, the secondary endpoint was Progression-free survival (PFS), Overall survival (OS) and Toxicity.

Results: Twenty-eight patients were enrolled between 08/2011 and 03/2017. Patients characteristics were: median age 69.5 years, male, 22(79%), ECOG PS of 0, 1, 2 or 1.3, and 1.5. The overall response rate was 22% with 6 partial responses, 8 stable diseases, 13 progression and 1 not evaluable yet. Median PFS was 4.6 months (95% CI: 2.0-7.0). Median OS was 9.6 months (95% CI: 2.3-16.9). Grade 3/4 toxicities included neutropenia in 36%, leukopenia in 16%, anemia in 11%, nausea/vomiting in 7%, febrile neutropenia in 7%, respectively. Tmab beyond progression (TBP) group (n = 20) did not differ from non-TBP group (n = 8) in PFS and OS (PFS: 5.0-2.8 months, p = 0.369, OS: 12.4-6.1 months, p = 0.363, log-rank test). And, in TBP group, therapeutic effect was associated with duration of PFS of 1-4 line Tmab combined therapy (≥6 months (n = 10), <6 months (n = 10), PFS: 6.4-8.2 months, p = 0.016, OS: Not reached≥6.5 months, p = 0.002, log-rank test).

Conclusions: Weekly paclitaxel plus trastuzumab appeared favorable and well tolerated as second-line chemotherapy for HER2-positive gastric cancer patients in this single arm study.

Legal entity responsible for the study: Toyama Prefectural Central Hospital

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Phase I dose escalation study with expansion cohort of the addition of nab-paclitaxel (nab-P) to capecitabine and oxaliplatin (CAPOX) as first line treatment of advanced esophageogastric adenocarcinoma (EGAC) (ACTION study)

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Background: The prognosis of advanced EGAC remains poor. Triplet containing taxanes show a survival benefit but at the cost of increased toxicity. Given the favorable toxicity profile of nab-P compared to conventional taxanes we conducted a phase I dose escalation study to find the maximum tolerated and recommended phase 2 dose (MTD/RP2D) of the addition of nab-P to CAPOX.

Methods: Patients (pts) with metastatic or non-resectable EGAC received oxaliplatin 65 mg/m2 day 1 and 8 and capecitabine 1000 mg/m2 bid day 1-14 in a 21 day cycle, with nab-P day 1 and 8 at 4 dose levels (DL1: 60, DL2: 80, DL3: 100 and DL4: 120 mg/m2, respectively) in a standard 3 + 3 design, followed by an expansion cohort of 20 pts. Tumor response was assessed every 3 cycles (RECIST 1.1). Pts were treated until progressive disease (PD), unacceptable toxicity or a maximum of 6 cycles after which capcitabine monotherapy was continued. Ox and nab-P were reintroduced if PD occurred after more than 3 months.

Results: We enrolled 26 pts (median age 63; 18 had esophageal cancer and 8 gastric cancer). Ten pts had received prior curative treatment. At DL1 and DL2 no dose limiting toxicity (DLT) occurred. At DL2 2 DLT’s occurred (diabetes and dehydration because of vomiting/diarrhea). MTD was established at 80 mg/m2 and chosen for evaluation in the expansion cohort. However, because of diarrhea grade 3 grade 3/2 pts (42%) in the course of treatment the nab-P dose was reduced to 60 mg/m2. Grade 3/4 toxicity of all pts treated at this DL was nausea (18%), diarrhea, vomiting, anorexia and elevated GGT (all 9%). Notable grade 1/2 toxicities were neuropathy (82%), dysgeusia, diarrhea (both 64%), nausea (55%) and vomiting (45%). Best responses were PR (13 pts), SD (9 pts) and PD (2 pts). Median follow-up is 9.1 months, 22 pts completed 6 cycles and 3...
Conclusions: Our data suggested HER2-positive AGC harbored KRAS mutations, confirming the predictive value of benefit as receiving HER2 targeted treatment. Further investigation was warranted to Yakult, Ono, Bayer and Lilly. All other authors have declared no conflicts of interest.

Disclosure: E. Shinozaki: Honoraria from Taiho, Merck Serono, Takeda, Chugai, F. Otsuka: Research grants from Bayer, Merck, Pfizer, Merck Serono, MSD, Nordic, and Roche All other authors have declared no conflicts of interest.

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Background: Trastuzumab targeted on HER2 has been shown to confer overall survival benefit adding to fluoropyrimidine (Fp) plus CDDP in HER2-positive advanced gastric cancer (AGC). HER2 is known to make the formation of heterodimer with EGFR, HER3 and HER4. HER2 containing heterodimer activates the common downstream in HER family was performed on archival samples of over 500 AGC between March 2011 and November 2015 we chose 100 patients including high copy gains in EGFR, JAK2, FGFR2, MET, VEGFA, KRAS, NRAS, and PIK3CA. One sample exhibited co-amplification of CD274 and PCDHD12G (encoding PD-L1 and PD-L2), in addition to concurrent amplification of ERBB2, JAK2, FGFR2, MET, KRAS, and PIK3CA. Microarray images of the spatial distribution of CNAs were presented.

Results: Detectable percentage (%): CNA: %32.57. Lauren intestinal subtype histology correlated strongly with higher % genomic changes compared to diffuse subtype histology (p = 0.0012). Tumors located in the GEJ/cardia proximal stomach also correlated with higher % genomic changes compared to gastric body/antrum tumors (p = 0.0028). A variety of oncogenic CNAs were observed across patients including high copy gains in EGFR, JAK2, FGFR2, MET, VEGFA, KRAS, NRAS, and PIK3CA. One sample exhibited co-amplification of CD274 and PCDHD12G (encoding PD-L1 and PD-L2), in addition to concurrent amplification of ERBB2, JAK2, FGFR2, MET, KRAS, and PIK3CA. FISH images of the spatial distribution of CNAs were presented.

Conclusions: The inherent spatial intra-tumoral heterogeneity of oncogenic CNAs with de novo disease presentation illustrates the challenges in gastric cancer therapy. Further study will offer insight into strategies on combinatorial and/or sequential targeted and immunotherapeutic approaches.

Legal entity responsible for the study: Joseph Chao

Funding: United States National Institutes of Health – National Cancer Institute

Disclosure: All authors have declared no conflicts of interest.

Background: T. Matsushima 1, T. Wakatsuki 1, I. Nakayama 1, Y. Imamura 2, M. Watanabe 2, T. Komatsu 2, T. Matsushima 1, T. Wakatsuki 1, I. Nakayama 1, Y. Imamura 2, M. Watanabe 2, T. Komatsu 2

Results: KRAS mutation incidence for the WNT pathway gene RNF43 was analysed in 674 gastric cancer samples. RXC004 was profiled in gastric, pancreatic and biliary PDX models carrying the RNF43 mutations and growth inhibition was correlated with WNT pathway inhibition. To support the clinical trial a patient selection strategy, based on detection of RNF43 mutations from a liquid biopsy, using MassArray mass spectrometry technology is described. Results: Bioinformatics data-mining of TCGA identified that the prevalence of RNF43 mutation in gastric cancer is 14-16%. A specific hot spot mutation (G659Vfs*41) has been identified, which accounts for ~90% of the RNF43 mutations. Profiling of RXC004 in RNF43 mouse models of gastric and pancreatic cancer shows the potential for monotherapy efficacy. In order to translate our findings to the clinic, we developed an assay suitable for detection of RNF43 mutations in circulating tumour DNA (ctDNA) from patient plasma. Multiplexed assays for RNF43 mutations, including the G659Vfs*41 hotspot, have been developed using MassArray technology. By converting to UltraSeek MassArray methodology we are targeting a sensitivity of 0.1% allelic frequency and specificity >99% in patient ctDNA.

69IP Inter-patient and intra-tumour heterogeneity of oncogenic copy number alterations (CNAs) in gastric and gastroesophageal junction (GEJ) adenocarcinomas

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Background: Intra-tumour heterogeneity is well recognized to be inherent in biomarker discovery for gastric cancer since the initial reporting of HER2 overexpression. The Cancer Genome Atlas (TCGA) has laid the groundwork for CNAs comprising the mutational landscape of gastric cancer. We aimed to investigate through a genomic single nucleotide polymorphism (SNP) array panel and fluorescence in-situ hybridization (FISH) inter-patient and intra-tumoral spatial heterogeneity of CNAs.

Methods: 41 gastric adenocarcinoma patient samples treated with upfront surgical resection were retrospectively identified from the City of Hope Biopspecimen Repository. CNAs of 891 cancer-related genes at 10-500K resolution and detection of 74 frequent somatic mutations in 9 genes of interest (BRCA, KRAS, EGFR, ERBB2, IDH2, PIK3CA, NRAS, TP53) were assayed using the Affymetrix Oncoscan™ platform. Genome wide coverage outside of the 891 cancer genes were provided at 300 Kb resolution along with genome wide LOH provided at 5-10 Mb resolution. For samples with multiple CNAs detected, FISH was pursued to define down to a single-cell level the spatial distribution of CNAs.

Results: 692P Identification of an RNF34 mutated gastric cancer patient population with potential sensitivity to porcine inhibitor RXC004 and development of a complimentary ctDNA liquid biopsy assay for patient screening

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Background: RXC004 is a small molecule PORCN inhibitor, entering first-in-human trials in 2017. PORCN inhibition has been shown to have potential for the treatment of molecularly selected pancreatic and colorectal cancers, as well as the ability to synergise with anti-PD1 checkpoint inhibition. The aim of this study was to identify additional patient segments predicted to benefit from treatment with a PORCN inhibitor.

Methods: Mutation incidence for the WNT pathway gene RNF34 was analysed in 674 gastric cancer samples. RXC004 was profiled in gastric, pancreatic and biliary PDX models carrying the RNF34 mutations and growth inhibition was correlated with WNT pathway inhibition. To support the clinical trial a patient selection strategy, based on detection of RNF34 mutations from a liquid biopsy, using MassArray mass spectrometry technology is described.

Results: Bioinformatics data-mining of TCGA identified that the prevalence of RNF34 mutation in gastric cancer is 14-16%. A specific hot spot mutation (G659Vfs*41) has been identified, which accounts for ~90% of the RNF34 mutations. Profiling of RXC004 in RNF34 mouse models of gastric and pancreatic cancer shows the potential for monotherapy efficacy. In order to translate our findings to the clinic, we developed an assay suitable for detection of RNF34 mutations in circulating tumour DNA (ctDNA) from patient plasma. Multiplexed assays for RNF34 mutations, including the G659Vfs*41 hotspot, have been developed using MassArray technology. By converting to UltraSeek MassArray methodology we are targeting a sensitivity of 0.1% allelic frequency and specificity >99% in patient ctDNA.
Conclusions: RXC004 is entering first-in-human trials in 2017 with a modular phase I/IIa clinical protocol design which allows for phase IIa expansion arms in molecularly selected patient segments including gastric cancer. We demonstrate that there is an RNA34 mutated patient segment which may benefit from therapy with RXC004, and that these patients have the potential to be identified by a ctDNA screening approach.

Clinical trial identification: EudraCT Number 2017-000720-98

Legal entity responsible for the study: Redx Pharma Plc

Funding: Redx Pharma Plc

Results: The SPARC expression in the tumor epithelia was higher than that in the non-tumorous epithelia in only 5 patients (11%), while negative or weaker SPARC staining in the tumor epithelia was observed in the remaining specimens. SPARC expression level in the CAF was classified into the following 3 categories: 1/3 or less (score 0), 1/3–2/3 (score 1), and 2/3 or more (score 2) of CAF were positive for SPARC (18 patients (38%), 11 (23%), and 18 (38%), respectively). There was no difference according to dichotomophological characteristics between CAF SPARC level (low vs. high). CAF SPARC level (low vs. high) was not associated with the progression-free survival (median, 4.8 vs. 3.0 months; P = 0.259), overall survival (median, 10.2 vs. 8.0 months; P = 0.419), time to treatment failure (median, 4.7 vs. 3.0 months; P = 0.291), and overall response rate (ORR = 0.450).

Conclusions: SPARC level was not correlated with efficacy of nab-PTX for GC. The results of this exploratory analysis do not support the possibility of SPARC expression level for clinical biomarker regarding nab-PTX in GC.

Clinical trial identification: UMIN Clinical Trials Registry Registration Number: UMIN000012247

Legal entity responsible for the study: Chubu Clinical Oncology Group

Funding: None

Disclosure: Y. Kodera: Honoraria: Olympus, Chugai Pharma, Lilly, Johnson & Johnson, Ajinomoto, Takeda, Yakult Honsha, Taiho Pharmaceutical, Otsuka, Kaken Pharmaceutical, Ono Pharmaceutical, Asahi Kasei, Covidien/Medtronic All other authors have declared no conflicts of interest.

697P Detection of microsatellite instability (MSI) with a novel panel of biomarkers in gastric cancer samples

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Background: Detection of microsatellite instability (MSI) is recommended to identify colorectal cancer (CRC) patients with Lynch syndrome, but MSI is present in several other tumor types such as ovarian and gastric cancer. Current clinical reference methods to detect MSI stain for mismatch repair proteins or analyze frequently mutated DNA repeat regions. The Idylla™ methodology is currently developed for a unique set of novel biomarkers (Zhao et al. 2014; eLITE) capable of faster detection with greater specificity and selectivity compared to current methods.

Methods: To assess the suitability of the novel marker set to detect MSI status in gastric cancer, we performed a small-scale evaluation study: 10 novel MSI biomarkers with proven efficacy in CRC were tested in 150 gastric cancer samples. Repeat length was determined on FFPE DNA by PCR followed by melting curve analysis. Eighty-five samples were screened with a reference methodology for MSI detection (Promega MSI analysis system).

Results: Fifteen out of 150 samples (10%) were classified as MSI-H with the novel set of biomarkers. At least 5/10 (50%) of the markers scored mutant in each of these 15 samples. All of the 10 markers scored wild type in 131/150 samples. All samples with at least one mutant marker (n = 19) and 66 randomly selected samples with no mutant markers were screened with the Promega MSI analysis system. 985 samples failed with the reference method, even after repeat testing, while the Idylla™ methodology did not generate any failures (0/150). For 76 samples with results available for both methods, the overall percent agreement was 100% (76/76).

Conclusions: Fifteen out of 150 samples (10%) were classified as MSI-H with the novel set of biomarkers. At least 5/10 (50%) of the markers scored mutant in each of these 15 samples. All of the 10 markers scored wild type in 131/150 samples. All samples with at least one mutant marker (n = 19) and 66 randomly selected samples with no mutant markers were screened with the Promega MSI analysis system. 985 samples failed with the reference method, even after repeat testing, while the Idylla™ methodology did not generate any failures (0/150). For 76 samples with results available for both methods, the overall percent agreement was 100% (76/76).

Legal entity responsible for the study: Biocartis NV, Mechelen, Belgium

Funding: EMD Serono Research & Development Institute, Inc.


698P Correlation between SPARC expression and efficacy of nab-paclitaxel for advanced gastric cancer refractory to fluoropyrimidine: An exploratory analysis of a phase II trial, CC01/003

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Background: Secreted protein acidic and rich in cysteine (SPARC) reportedly influences the response to albumin-bound paclitaxel due to its characteristics of albumin-binding matrix associated protein that may enhance the drug accumulation in the tumor tissue. However, its role in gastric cancer (GC) has been controversial. In this study, correlation between SPARC expression and the efficacy of nab-paclitaxel (nab-PTX) for GC was evaluated to explore its potential as a predictor of sensitivity.

Methods: In a multi-institutional prospective phase II trial (CC01/003), efficacy of nab-PTX under a modified dose reduction criteria was evaluated in 47 advanced GC patients refractory to fluoropyrimidine. Correlation between SPARC expression on immunohistochemistry (IHC) was evaluated as a predictor of sensitivity in an exploratory analysis in the CC01/003 trial. SPARC staining was scored in two compartments: cancer associated fibroblasts (CAF) in the tumor stroma and tumor epithelial cells.

Results: The SPARC expression in the tumor epithelia was higher than that in the non-tumorous epithelia in only 5 patients (11%), while negative or weaker SPARC staining in the tumor epithelia was observed in the remaining specimens. SPARC expression level in the CAF was classified into the following 3 categories: 1/3 or less (score 0), 1/3–2/3 (score 1), and 2/3 or more (score 2) of CAF were positive for SPARC (18 patients (38%), 11 (23%), and 18 (38%), respectively). There was no difference according to dichotomophological characteristics between CAF SPARC level (low vs. high). CAF SPARC level (low vs. high) was not associated with the progression-free survival (median, 4.8 vs. 3.0 months; P = 0.259), overall survival (median, 10.2 vs. 8.0 months; P = 0.419), time to treatment failure (median, 4.7 vs. 3.0 months; P = 0.291), and overall response rate (ORR = 0.450).

Conclusions: SPARC level was not correlated with efficacy of nab-PTX for GC. The results of this exploratory analysis do not support the possibility of SPARC expression level for clinical biomarker regarding nab-PTX in GC.

Clinical trial identification: UMIN Clinical Trials Registry Registration Number: UMIN000012247

Legal entity responsible for the study: Chubu Clinical Oncology Group

Funding: None

Disclosure: Y. Kodera: Honoraria: Olympus, Chugai Pharma, Lilly, Johnson & Johnson, Ajinomoto, Takeda, Yakult Honsha, Taiho Pharmaceutical, Otsuka, Kaken Pharmaceutical, Ono Pharmaceutical, Asahi Kasei, Covidien/Medtronic All other authors have declared no conflicts of interest.
A dose-response study of ramucirumab treatment in patients with gastric cancer/gastroesophageal junction adenocarcinoma: Primary results of 4 dosing regimens in the phase 2 trial HT-EC-JVDB


Background: Ramucirumab (RAM) is approved for the treatment of advanced gastric cancer or gastroesophageal junction adenocarcinoma with disease progression after prior platinum and/or fluoropyrimidine chemotherapy at 8 mg/kg every 2 weeks (Q2W) based on results of 2 phase 3 trials. Exposure-response analyses from these trials indicated efficacy of RAM correlated with exposure. JVDB is an open-label RAM monotherapy study that examined pharmacokinetics (PK) and safety of the standard and 3 higher exposure regimens.

Methods: Patients (n = 106) were randomized 1:1:1:1 to 4 treatment arms: 8 mg/kg Q2W (Arm 1), 12 mg/kg Q2W (Arm 2), 6 mg/kg every week (Arm 3), and 8 mg/kg Days 1 and 8 (D1D8) every 3 weeks (Q3W) (Arm 4). PK was collected from all groups. Treatment-emergent adverse events (TEAEs) were graded by NCI CTCAE v4.0. Tumor response was assessed by RECIST 1.1.

Results: Mean RAM trough and peak concentrations are shown (Table). Median (months) progression-free survival (PFS) was similar across all arms (Arm 1 = 1.45; Arm 3 = 1.54; Arm 4 = 1.51), with the exception of Arm 2 = 2.50. PFS hazard ratio (HR) for Arm 2 vs 1 = 0.82; Arm 3 vs 1 = 0.88; Arm 4 vs 1 = 0.57. Overall survival (OS) HR for Arm 2 vs 1 = 0.70; Arm 3 vs 1 = 0.95; Arm 4 vs 1 = 0.90. The most common TEAEs were fatigue (22.4%), decreased appetite (21.1%), abdominal pain (18%), and vomiting (18%), consistent with the REGARD trial.

Comparative analysis of Ramucirumab in patients with advanced gastric or gastroesophageal adenocarcinoma: Results from the phase 2 trial HT-EC-JVDB


Background: Ramucirumab (RAM) is approved for the treatment of advanced gastric cancer or gastroesophageal junction adenocarcinoma with disease progression after prior platinum and/or fluoropyrimidine chemotherapy at 8 mg/kg every 2 weeks (Q2W) based on results of 2 phase 3 trials. Exposure-response analyses from these trials indicated efficacy of RAM correlated with exposure. JVDB is an open-label RAM monotherapy study that examined pharmacokinetics (PK) and safety of the standard and 3 higher exposure regimens.

Methods: Patients (n = 106) were randomized 1:1:1:1 to 4 treatment arms: 8 mg/kg Q2W (Arm 1), 12 mg/kg Q2W (Arm 2), 6 mg/kg every week (Arm 3), and 8 mg/kg Days 1 and 8 (D1D8) every 3 weeks (Q3W) (Arm 4). PK was collected from all groups. Treatment-emergent adverse events (TEAEs) were graded by NCI CTCAE v4.0. Tumor response was assessed by RECIST 1.1.

Results: Mean RAM trough and peak concentrations are shown (Table). Median (months) progression-free survival (PFS) was similar across all arms (Arm 1 = 1.45; Arm 3 = 1.54; Arm 4 = 1.51), with the exception of Arm 2 = 2.50. PFS hazard ratio (HR) for Arm 2 vs 1 = 0.82; Arm 3 vs 1 = 0.88; Arm 4 vs 1 = 0.57. Overall survival (OS) HR for Arm 2 vs 1 = 0.70; Arm 3 vs 1 = 0.95; Arm 4 vs 1 = 0.90. The most common TEAEs were fatigue (22.4%), decreased appetite (21.1%), abdominal pain (18%), and vomiting (18%), consistent with the REGARD trial.

Conclusion: Trough concentrations of the 3 experimental regimens were greater than the standard regimen. Arm 2 displayed the highest peak RAM concentration. Though efficacy was not different, some trends toward improved PFS were noted versus the standard regimen were observed. Despite higher RAM exposures observed with the alternative regimens, safety profiles were comparable to the standard regimen.

Clinical trial identification: NCT02443883

Legal entity responsible for the study: Eli Lilly and Company

Funding: Eli Lilly and Company

Disclosure: J.A. Ajanf: Honoraria: Lilly, Bayer, Novartis, Five Prime Therapeutics, Taio, Genentech, Celgene Funding: Novartis, BMS, Taio, Genentech, MedImmune, Amgen, Lilly, Merck, Deltra-Ph, Gilead Sciences, Takeda, Celgene. M. Shenker: Corporate-sponsored research, meaning international clinical trials (like JVDB trial), for which I have financial contract as PI. Eli Lilly, Pfizer, Roche, Novartis, BMS, MSD, Merck Serono, Boehringer Ingelheim, Amgen, Astellas, Mylan. C. Tourgand: Honoraria from Eli Lilly. D. Fergy, Y. Zhang, A. Long, W.L. Kuo, L. Gao, J. Kuhf: Employee of Eli Lilly. All other authors have declared no conflicts of interest.

The effectiveness of the 8th American Joint Committee on Cancer TNM classification in the prognosis evaluation of stage III gastric cancer patients: A comparative study between the 7th and 8th editions


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Background: The 8th edition of the AJCC TNM staging system for gastric cancer was released in 2016 and included major revisions, especially of stage III. We aimed to compare the prognostic value of the seventh and eighth editions of the AJCC/TNM classification for stage III gastric cancer.

Methods: Clinical data on 1,579 patients operated on for stage III gastric cancer according to the seventh edition between December 2008 and November 2014 were analyzed and the 7th and 8th TNM classifications were compared in terms of prognostic performance.

Results: According to the 8th AJCC/TNM classification, the 5-year overall survival rates of IB, IIB and IIC were 49.4%, 29.6% and 15.2%, respectively (P < 0.001). The median number of lymph nodes (LNs) resected was 33 (range 5–112), and the optimal cut-off value for the number of LNs resected was 30. Cox regression multivariate analysis showed the 8th AJCC N classification, 8th AJCC T classification, tumor size, lymphatic vessel invasion, and number of LNs removed were independent prognostic factors. However, the 7th edition classification had higher c-index, linear trend and likelihood ratio2 scores, and smaller AIC values compared with those for the 8th edition, which represented the optimum prognostic stratification. Further subgroup analysis found that the 8th staging system generated the best prognostic stratification only when LNs removed >30.

Conclusions: The 8th TNM classification provide better accuracy than 7th edition in predicting the stage III gastric cancer with LNs harvested >30.

Legal entity responsible for the study: Changming Huang

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Comparison of prognostic models for hepatocellular carcinoma (HCC) in patients treated with the sorafenib: Results from a Canadian multicenter HCC database


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Background: Several staging systems and models (TNM, BCLC, Okuda, CLIP and ALBI) have been developed to estimate the prognosis of patients with HCC. Most of these were developed prior to the prevalent use of sorafenib. The purpose of this study was to compare the prognostic and discriminatory power of these models in predicting survival for HCC patients treated with sorafenib.

Methods: Patients who received sorafenib for the treatment of HCC between January 1, 2008 and June 30, 2015 in the provinces of British Columbia and Alberta, as well as Princess Margaret Cancer Centre and Sunnybrook Odette Cancer Centre in Toronto, Ontario were included. Survival outcomes for each model were assessed with Kaplan-Meier (KM) curves and compared with the log-rank test. Time dependent area under the curve (t-AUC) was used to test the discriminatory power of each model (higher t-AUC = more discriminatory power). Akaike information criterion (AIC), a measure of goodness-of-fit of models while penalizing overly complex models, was used to compare the models (lower AIC = better model).

Results: A total of 681 patients were included in this analysis. Median age was 64 years (range 8-91). Majority were males (80%), had a Child-Pugh score A (86%), ECOG performance status 0 (30%) and 1 (60%). 37% of patients were of East Asian ethnicity. Most common etiology for liver disease was hepatitis B (33%) and C (29%). At the start of sorafenib, most patients were BCLC stage C (92%) and TNM stage IV (61%). The median overall survival for the entire cohort was 9.2 months (95% CI 8.9–10.4). CLIP had the highest t-AUC and the lowest AIC. See table below for t-AUC and AIC results.

<table>
<thead>
<tr>
<th>Model</th>
<th>t-AUC (95% CI)</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLIP</td>
<td>0.659 (0.601 – 0.718)</td>
<td>5725.76</td>
</tr>
<tr>
<td>Okuda</td>
<td>0.645 (0.597 – 0.694)</td>
<td>5730.38</td>
</tr>
<tr>
<td>ALBI</td>
<td>0.558 (0.510 – 0.599)</td>
<td>5756.73</td>
</tr>
<tr>
<td>BCLC</td>
<td>0.558 (0.518 – 0.599)</td>
<td>5759.25</td>
</tr>
<tr>
<td>TNM stage</td>
<td>0.561 (0.499 – 0.623)</td>
<td>5771.51</td>
</tr>
</tbody>
</table>

Conclusions: According to our large multi-center study, CLIP appears to be the most informative in predicting survival in HCC patients treated with sorafenib. Prospective studies are needed to determine its role in patient selection for clinical trials and in guiding treatment decisions. The TNM and BCLC staging systems were the least useful in predicting survival in this population.

Legal entity responsible for the study: CHORD Consortium

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Background: Therapeutic outcomes for patients (pts) with advanced hepatocellular carcinoma (HCC) are currently poor, despite the introduction of new therapies. c-Met is a potential therapeutic target in HCC, and c-Met inhibitors have demonstrated activity in preclinical HCC models. Tepotinib (MSI2186193) is a highly selective c-Met inhibitor that has favorable safety and promising clinical activity, particularly against c-Met+ solid tumors. We report the final results of a phase Ib trial of tepotinib in pts with advanced HCC.

Methods: Enrolled pts were Asian adults with confirmed HCC of BCLC Stage C, Child-Pugh Class A liver function without encephalopathy, and ECOG PS 0–2. Pts received tepotinib 300, 500 (the RP2D), or 1,000 mg/day on a 21-day cycle. c-Met expression was retrospectively determined by IHC (c-Met+ defined as ≥50% tumor HIC2+/3+). The primary objective was to confirm the recommended phase II dose (RP2D) of tepotinib.

Results: No dose-limiting toxicities were observed in the 27 pts enrolled (median age 57 [38–69]; male 23; ECOG PS 0/1/11/6), who received tepotinib 300 mg/day (n = 7), 500 mg/day (n = 14), or 1,000 mg/day (n = 6, with dose reduction). 22 pts had treatment-emergent adverse events (TRAEs), most commonly diarrhea (n = 10), nausea (n = 8), elevated AST (n = 7), and elevated ALT (n = 6). The most common grade ≥3 TRAEs were AST elevations (n = 3), elevated ALT (n = 3), and elevated lipase (n = 5). Best overall response (BOR) was partial response (PR) in 2 pts, of duration 19.0 months (500 mg/day) and 4.4 months (1,000 mg/day). 8 pts had a BOR of stable disease (SD); 14 pts had PD, 1 pt had Non-CR/Non-PR, 2 pts were not evaluable. 5 pts had progression-free survival > 12 months. Tumor c-Met status was available for 26 pts; of 7 pts with c-Met+ tumors, 2 had a PR and 2 had SD. PR and exploratory biomarker were investigated.

Conclusions: Tepotinib had antitumor activity in Asian pts with advanced HCC, particularly those with c-Met+ tumors, and was well tolerated at doses up to 1,000 mg/day. A maximum tolerated dose was not defined. The efficacy and safety of first-line tepotinib in pts with c-Met+ HCC are being compared with those of sorafenib in the phase II part of this study.

Clinical trial identification: NCT01988493

Legal entity responsible for the study: Merck KGaA

Disclosure: D. Zhou, C. Zhao, A. Becker: Employee of Merck. All other authors have declared no conflicts of interest.

Table: 702P

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>mOS, days</th>
<th>Simulated data Mean (SD) of mOS, days</th>
<th>mTTP, days</th>
<th>Simulated data Mean (SD) of mTTP, days</th>
<th>RR</th>
<th>Simulated data Mean (SD) of RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHARP</td>
<td>Sorafenib</td>
<td>327</td>
<td>329 (26.5)</td>
<td>119</td>
<td>118 (10.1)</td>
<td>0.057</td>
<td>0.057 (0.013)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>243</td>
<td>245 (21.7)</td>
<td>82</td>
<td>83 (2.4)</td>
<td>0.023</td>
<td>0.023 (0.009)</td>
</tr>
<tr>
<td>AP</td>
<td>Sorafenib</td>
<td>198</td>
<td>198 (18.8)</td>
<td>84</td>
<td>85 (6.4)</td>
<td>0.033</td>
<td>0.033 (0.014)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>127</td>
<td>129 (14.5)</td>
<td>42</td>
<td>42 (2.5)</td>
<td>0.013</td>
<td>0.013 (0.013)</td>
</tr>
</tbody>
</table>

m, median; SD, standard deviation

Simulated data based on patient-level data from the phase 3 SHARP and AP trials in patients with advanced HCC randomized to sorafenib (SOR) or placebo (PBO).

Methods: A bootstrap approach was applied to simulate 10,000 trials of patients with advanced HCC. From SHARP (N = 602; NCT00105443) and AP (N = 226; NCT00892792), RR was measured by investigator assessment per RECIST with SHARP–BCLC amendments (Reig et al. Semin Liver Dis 2014) prior to crossover of PBO subjects to sorafenib treatment. Pearson correlation was calculated between estimated median OS (mOS) and estimated median TTP (mTTP) estimated RR for the SOR and PBO arms separately. Pearson correlation of log-rank test statistics comparing SOR and PBO were calculated for OS and TTP, Cochran–Mantel–Haenszel test statistic comparing the 2 arms for RR was also evaluated.

Results: The mean of mOS, mTTP, and RR from simulated trials was similar to that reported in SHARP and AP (Table). The correlation between mOS and mTTP was 0.37 for SOR and 0.218 for PBO in SHARP, and 0.315 for SOR and 0.258 for PBO in AP; the correlation of log-rank test statistics comparing SOR and PBO was 0.387 in SHARP and 0.581 in AP. In SHARP, the correlation between mOS and RR was 0.174 for SOR and 0.051 for PBO; the correlation of test statistics comparing SOR and PBO was 0.136. In AP, the correlation between mOS and RR was 0.138 for SOR and 0.099 for PBO; the correlation of test statistics comparing SOR and PBO was 0.211.

Conclusions: The simulated data were representative of patient population data in the SHARP and AP trials for mOS, mTTP, and RR. Our analysis showed a weak correlation between OS and TTP/RR in these trials, suggesting that TTP and RR by RECIST are not reliable surrogate endpoints for OS in patient with advanced HCC.

Clinical trial identification: NCT01105443; NCT00492752.

Legal entity responsible for the study: Bayer

Funding: Bayer


Cost effectiveness of selective internal radiation therapy (SIRT) with Y-90 resin microspheres versus sorafenib in Barcelona Clinic Liver Cancer (BCLC) stage C hepatocellular carcinoma patients in the UK

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Background: Recently presented pivotal trial data (Vigrahn et al. International Liver Congress 2017) has shown that there is no significant difference in overall survival between selective internal radiation therapy (SIRT) with Y-90 resin microspheres (SIR-Spheres), Sirtex Medical, North Sydney, Australia) and sorafenib for patients with Barcelona Clinic Liver Cancer (BCLC) stage C liver-located or liver-predominant hepatocellular carcinoma. Y-90 resin microspheres are, however, safer and better tolerated by patients than sorafenib, as well as reducing costs, due to single administration and less frequent and severe side effects. Our aim was to evaluate the cost effectiveness of SIRT using Y-90 resin microspheres versus sorafenib for the treatment of patients with BCLC stage C hepatocellular carcinoma in the UK.

Methods: A cost-minimisation model was built, with equal efficacy assumed between SIRT and sorafenib. Adverse events data were collected from the Phase III SHARP trial for sorafenib (Llovet et al. N Engl J Med 2008;359:378–90) and from the ENRY study for Y-90 resin microspheres (Sangro et al. Hepatology 2011;54:868–78). Treatment costs were taken from standard UK sources and real-world data from a UK hospital: treatment and adverse events disutilities were taken into account.
abstracts
from published literature. Inputs were validated by UK clinicians and one-way and
probabilistic sensitivity analyses were performed.
Results: SIRT using Y-90 resin microspheres is dominant versus sorafenib, providing
greater quality-adjusted life years (QALYs) at a lower cost. Y-90 resin microspheres
provide 0.0079 (95% confidence interval [CI] 0.0046–0.0111) more QALYs than sorafenib, while saving £8,909 (95% CI £3,257–£14,570). One-way sensitivity analysis
showed time on treatment for sorafenib and the work-up and administration costs of
Y-90 resin microspheres to be the parameters with the largest influence on results.
Conclusions: In the case of equal efficacy between Y-90 resin microspheres and sorafenib, SIRT using Y-90 resin microspheres is a cost-effective therapy for BCLC stage C
hepatocellular carcinoma patients in the UK.
Legal entity responsible for the study: BresMed Health Solutions Ltd
Funding: Sirtex
Disclosure: D. Palmer: Research grants, consultant, sponsored lectures: Sirtex and
Bayer. P. Ross: Grants: Sanofi, consultant: Bayer, Celgene Sirtex, sponsored lectures:
Bayer, Celgene, Merck, Roche. Travel and meeting attendance: Merck, Bayer, Celgene,
Amgen and Servier. T. Shah: Grants: Novartis, and consulted Sirtex. D. Yu: Consultant:
Bayer, Boston Scientific, Gore Medical, Sirtex and St Jude Medical. Lectures sponsored:
Bayer, Boston Scientific, Gore Medical, Sirtex and St Jude Medical. S. Shergill:
Employee of Sirtex. K. Patterson, N. Brereton, D. Lee: Reimbursed for work presented
here by Sirtex

704P

Annals of Oncology
Methods: Valid biomarker data were available for 343/573 patients. Expression levels of
750 plasma miRNAs collected at baseline were quantified by qPCR. To be eligible,
miRNAs had to be measurable on a continuous scale or dichotomized by pre-processing
(present vs absent), and present in  5% of patients (i.e. n  18). The predictive and prognostic effects (HR and 95% CI) were evaluated using a Cox proportional hazards model
with miRNAs as continuous or dichotomized variables. A predictive effect was modeled
as an miRNA–treatment interaction effect and subjected to Akaike information criterion
(AIC)-based selection to assess its association with OS and TTP.
Results: Demographic covariates were generally similar in the overall RESORCE and
miRNA biomarker cohorts, except the latter had a smaller proportion of Asian patients.
Of the 750 miRNAs analyzed, 25 showed a multiplicity-adjusted prognostic effect
(P  0.05) for OS. Nine miRNAs showed a multiplicity-adjusted predictive effect
(P  0.05) for OS; 3 of the 9 predictive markers were also prognostic (Table). No
miRNA was found to be predictive for TTP.

Table: 705P
miRNA

HR (95% CI)
hsa-miR-15b-3p
hsa-miR-107
hsa-miR-320b
hsa-miR-122-5p
hsa-miR-374b-3p
hsa-miR-200a-3p
hsa-miR-30a-5p
hsa-miR-125b-5p
hsa-miR-645

Ang-2 polymorphisms in relation to outcome in advanced HCC
patients receiving sorafenib

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Background: Sorafenib, an oral multikinase inhibitor, represents the standard care for
advanced hepatocellular carcinoma. Angiopoietin-2 (Ang-2) is a crucial angiogenic
factor. By binding to its receptor Tie2, Ang-2 cooperates with the VEGF pathway to
maintain normal physiological functions. In the presence of VEGF, Ang-2 destabilizes
blood vessels and promotes vascular sprouting. In cancers, Ang-2 is linked to not only
angiogenesis but also invasive and metastatic phenotypes. Although sorafenib exerts no
significant activity against Tie2, the predictive value of Ang-2 has been explored in 2
studies. The actual role of Ang-2 in predicting sorafenib efficacy warrants further investigations. Polymorphism analysis seems to have more advantages than protein or gene
expression analysis. In our study we analysed the role of ANG-2 polymorphisms in relation to clinical outcome in patients with hepatocellular carcinoma treated with
sorafenib.
Methods: We analyzed 135 patients with hepatocellular carcinoma treated with sorafenib. Peripheral blood samples or FFPE tumor tissues were available for DNA extraction
and genotyping analysis. Nine Ang-2 polymorphisms were analyzed by direct sequencing or Real Time PCR method.
Results: With regard to Ang4 rs55633437 was observed that patients carrying the allele
GG were associated with a better PFS and OS. The variants GG were associated with a
median OS of 16.9 months vs 6.5 months of variants GT and TT (p ¼ 0.016). The variants GT and TT were associated with a median PFS of 2.94 months vs 4.67 months of
variants GG (p ¼ 0.03). These data were confirmed by multivariate analysis.
Conclusions: Ang4 rs55633437 could represent prognostic markers in patients with
advanced hepatocellular carcinoma treated with sorafenib.
Legal entity responsible for the study: IRST-IRCCS
Funding: None
Disclosure: All authors have declared no conflicts of interest.

705P

Circulating miRNA biomarkers predicting regorafenib (REG) clinical
benefit in patients with hepatocellular carcinoma (HCC) in the
RESORCE trial

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1

Background: REG improved overall survival (OS) and time to progression (TTP) versus placebo in patients with HCC who progressed during prior sorafenib in the phase 3
RESORCE trial (Bruix et al, Lancet 2017). This exploratory analysis evaluated the potential of circulating miRNA plasma biomarkers to predict the OS and TTP benefit
with REG in RESORCE.

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miRNA predictive for OS

0.37 (0.20, 0.70)
0.54 (0.37, 0.81)
0.57 (0.41, 0.81)
1.35 (1.14, 1.60)
1.36 (1.11, 1.65)
1.39 (1.15, 1.68)
1.47 (1.14, 1.88)
1.54 (1.19, 1.99)
3.16 (1.52, 6.55)

miRNA prognostic for OS

P-value
0.05
0.05
0.05
0.05
0.05
0.05
0.05
0.05
0.05

P-value
0.01
0.06
0.01
0.39
0.06
0.03
0.34
0.32
0.06

Conclusions: This exploratory analysis suggests that multiple miRNAs may be potentially predictive for OS in patients treated with REG. The biological role of the miRNAs
in HCC as well as their potential functional correlation to treatment benefit needs to be
analyzed further.
Clinical trial identification: NCT01774344
Legal entity responsible for the study: Bayer
Funding: Bayer
Köchert: Employment: Bayer. R.S. Finn: Consulting and Advisory Role: Bayer, Pfizer,
Novartis, BMS, Eisai. J.M. Llovet: Research/Education Grant: Bayer, Blueprint
Medicines, BI, Incyte Advisory Board: Bayer, Eisai, BMS, Eli Lilly Consulting: Eli Lilly,
Bayer, BMS, Blueprint Medicines, Eisai, Celsion, BI. J. Bruix: Research/Education
Grant: Daiichi Sankyo, ArQule, Bayer, Sirtex. Honoraria: Gilead, AbbVie, Kowa, Bayer,
BTG, ArQule, Terumo, Sirtex, BMS, Eisai, BI, Novartis, OSI, Roche, Onxeo. Advisory
Board: Bayer, Kowa, BTG, ArQule, Terumo, Sirtex, BMS, Eisai, Novartis, OSI, Roche,
Onxeo. Consulting: Gilead, AbbVie, Kowa, Bayer, BTG, ArQule, Terumo, Sirtex, BMS,
BI, Kowa, Novartis, OSI, Roche, Onxeo, Daiichi Sankyo, Abbot, Glaxo, Eli Lilly.

706P

Overall survival (OS) by platelet count at baseline in patients with
hepatocellular carcinoma (HCC) treated with sorafenib (SOR) in the
SHARP and AP trials and regorafenib (REG) in the RESORCE trial

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Background: SOR and REG significantly improved OS versus placebo (PBO) in patients with unresectable HCC: SOR in the first-line setting in both the SHARP (median
OS: 10.7 SOR vs 7.9 months PBO, HR 0.69; P < 0.001) and AP trials (median OS: 6.5
SOR vs 4.2 months PBO, HR 0.68; P ¼ 0.014); and REG in patients who progressed
during prior SOR in the RESORCE trial (median OS: 10.6 REG vs 7.8 months PBO, HR
0.63; P < 0.0001). This exploratory analysis evaluated OS by baseline platelet count in
HCC in the SHARP, AP, and RESORCE trials.
Methods: Patients with advanced HCC who received treatment in SHARP (SOR
n ¼ 299, PBO n ¼ 303; NCT00105443), AP (SOR n ¼ 150, PBO n ¼ 76;
NCT00492752), and RESORCE (REG n ¼ 374, PBO n ¼ 193; NCT01774344) were
included in the analysis. Patients were subgrouped according to a baseline platelet
count of > 150  109/L and 150  109/L. OS (HR and its 95% CI) was evaluated using
a Cox proportional hazards model.

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Clinical trial identification: 

ment options in HCC regardless of platelet count at baseline. 

first-line HCC but not for second-line HCC patients. SOR and REG are effective treat- 

OS over PBO in both subgroups. 

improved OS, but this was not observed in RESORCE. Both SOR and REG improved 

os and extrahepatic spread, less tumor burden, and more cases of 

hypertension C. In SHARP and AP, a lower platelet count at baseline was associated with 

proved OS, respectively (Table).

Results: 

In SHARP, 180 patients (60%) treated with SOR and 199 (66%) receiving 

PBO had a baseline platelet count of > 150 × 10^9/L; 84 (56%) with SOR and 46 (61%) 

with PBO in AP; 165 (44%) with REG and 91 (47%) with PBO in RESORCE. Baseline 

variables were generally similar between subgroups for AP; in RESORCE, more patients 

had hematosis C in the > 150 × 10^9/L platelet count group, in SHARP, the lower platelet 

count group had more patients with ECOG PS 0 and BCLC B, fewer patients with mac- 

rovascular invasion and extraparenchymal spread, less tumor burden, and more cases of 

hepatosis C. In SHARP and AP, a lower platelet count at baseline was associated with 

improved OS, but this was not observed in RESORCE. Both SOR and REG improved 

OS over PBO in both subgroups. 

Conclusions: 

The analysis indicates that platelet count may be a prognostic factor for 

first-line HCC, but not for second-line HCC patients. SOR and REG are effective treat- 

ment options in HCC regardless of platelet count at baseline.

Clinical trial identification: NCT01774344 

Legal entity responsible for the study: Bayer 

Funding: Bayer 


707P Network meta-analysis (NMA) of treatments for unresectable hepatocellular carcinoma (uHCC) 

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Background: In a phase 3 randomized controlled study (RCT) lenvatinib (LEN) dem- 

onstrated significantly better progression-free survival (PFS) vs sorafenib (SOR) in treat- 

ment-naive (1L) uHCC patients. Prior SOR RCTs had been conducted vs placebo (PBO). Our aim was to synthesize all efficacy evidence enabling a comparison of both 

LEN and SOR to PBO. 

Methods: EMBASE®, MEDLINE®, MEDLINE® in-process, and Cochrane databases were systematically searched through February 2017 for relevant RCTs in 1L uHCC. 

Data from the recently completed LEN RCT were added to the review. A conventional 

NMA based on PFS and overall survival (OS) was performed using a frequentist random 

effect NMA programmed in R 3.3.1. PBO was used as the reference treatment. 

Results: 3 Studies met inclusion criteria: 1 recently completed LEN vs SOR study (N = 954) and 2 RCTs comparing SOR to PBO (1) Llovet 2008 (N = 602) and (2) Cheng 2009 (N = 226). The 3 RCTs were generally comparable with some variability in patient baseline characteristics: mean age, years (63, 66, 61), % male (84, 87, 85), % 

POSitive serology for hepatitis B virus and C was found in respectively, 5 (16.6%) 

and 2 (6.6%) patients; with 1 co-infection. Chronic alcoholism was noted in 33.3%, 

diabetes and obesity were both present in 26.6% of cases. Alpha-fetoprotein, carbo- 

hydrate antigen 19-9 and carcinoembryonic antigen serum levels were above nor-

mal in 37-88%. Cirrhosis was associated in one third of cases. Systemic treatments are not stand-

ardized and must be evaluated in a dedicated study. 

The main clinical, biological, treatment and follow up data were reported. Statistical 

analysis was performed using Graph Pad Prism 6. 

Results: Thirty patients were included (76.6% of men, median age 64 years [extreme 

37-80]). Cirrhosis was associated in 33.3% of cases (Child-Pugh score A: 70%). 

Positive serology for hepatitis B virus and C was found in respectively, 5 (16.6%) 

and 2 (6.6%) patients; with 1 co-infection. Chronic alcoholism was noted in 33.3%, 

diabetes and obesity were both present in 26.6% of cases. Alpha-fetoprotein, carbo- 

hydrate antigen 19-9 and carcinoembryonic antigen serum levels were above normal in respectively 39% (median = 5.3 μg/L [2 – 21.47]) 50% (median = 21.8 IU/ 

mL [4.5-20 000]) and 14% (median = 2.4 μg/L [2-88]) of cases. Six patients (20%) 

were initially treated by surgical resection. At the diagnosis of advanced disease, 

66.6% of patients had multifocal hepatic lesions, 50% distant metastases (bone 

23.3%), lung (20%), peritoneal metastases (13.3%). Twenty-seven patients (90%) 

received first line of systemic treatment. Twenty-four patients were treated by 

chemotherapy: Gemcitabine (Gem) alone (n = 1), Gem + oxaliplatin (Gemox) 

(n = 12), Gem + bevazucimab (n = 9), Gem + cisplatin (n = 2). Two patients received chemoembolization, 1 patient received sorafenib. Twenty-one (70%) and 

4 (13.3%) patients had a second and third line of treatment, respectively. Median OS was 14.5 months. 

Conclusions: Advanced cHCC-ICC appear to be aggressive tumors with a poor prog-

nosis. Cirrhosis was associated in one third of cases. Systemic treatments are not stand-

ardized and must be evaluated in a dedicated study. 

Legal entity responsible for the study: Dr. Yann Toucheufu 

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Disclosure: All authors have declared no conflicts of interest. 

708P Epidemiological study of histologically proven advanced hepatocellular carcinoma: An AGEO multicenter retrospective study 

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Background: Hepatocellular carcinoma (cHCC-ICC) is a rare primary hepatic tumor combining the features of cholangiocarcinoma and hepatocellular carcinoma. Few data about the epidemiology of cHCC-ICC have been reported, mainly from surgical 

cases in Asian and American populations. The aim of this study was to evaluate epi-

demiological features and overall survival (OS) of histologically proven advanced 

cHCC-ICC patients. 

Methods: Data from patients treated for histologically proven cHCC-ICC in six French university hospitals between 2008 and February 2017, were retrospectively collected. 

Table: 706P

<table>
<thead>
<tr>
<th>Trial (active drug)</th>
<th>Platelet count</th>
<th>n</th>
<th>Median OS for active drug, days</th>
<th>Median OS PBO, days</th>
<th>HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHARP (SOR) &gt;150 × 10^9/L</td>
<td>379</td>
<td>290</td>
<td>218</td>
<td>0.81 (0.63, 1.04)</td>
<td></td>
</tr>
<tr>
<td>AP (SOR) ≤150 × 10^9/L</td>
<td>221</td>
<td>442</td>
<td>297</td>
<td>0.60 (0.42, 0.85)</td>
<td></td>
</tr>
<tr>
<td>RESORCE (REG) &gt;150 × 10^9/L</td>
<td>130</td>
<td>186</td>
<td>119</td>
<td>0.62 (0.42, 0.93)</td>
<td></td>
</tr>
<tr>
<td>≤150 × 10^9/L</td>
<td>95</td>
<td>227</td>
<td>166</td>
<td>0.78 (0.47, 1.31)</td>
<td></td>
</tr>
</tbody>
</table>

*HR < 1 indicates superior OS of REG over PBO.

Table: 707P

<table>
<thead>
<tr>
<th>Intervention</th>
<th>PFS HR (95% CI)</th>
<th>OS HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO – Comparator</td>
<td>0.38 (0.30, 0.49)</td>
<td>0.63 (0.50, 0.80)</td>
</tr>
<tr>
<td>LEN</td>
<td>0.58 (0.47, 0.70)</td>
<td>0.69 (0.57, 0.83)</td>
</tr>
<tr>
<td>SOR</td>
<td>1.52 (1.30, 1.76)</td>
<td>1.09 (0.94, 1.26)</td>
</tr>
<tr>
<td>LEN – Comparator</td>
<td>2.63 (2.06, 3.36)</td>
<td>1.58 (1.25, 2.00)</td>
</tr>
</tbody>
</table>
A Phase II study of sorafenib and yttrium-90 glass microspheres for advanced hepatocellular carcinoma, BLCc stage C

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Background: Combined use of sorafenib and local therapy for treating unresectable hepatocellular carcinoma (HCC) is not well established. Notably, most common cause of death in HCC is liver failure, therefore we tested the promise of controlling the local tumors even in the setting of advanced/metastatic disease to improve survival. Our study aimed to assess the efficacy and safety of combined use of sorafenib and yttrium-90 resin microspheres (Y90 RMS) in unresectable HCC, defined as Barcelona Clinic Liver Cancer class C.

Methods: Between October 2013 and August 2016 we enrolled 40 advanced stage HCC patients, 38 patients were treated with sorafenib followed (after 4 weeks) with Y90 RMS at MD Anderson Cancer Center. Survival analysis was done to evaluate median overall survival (OS) and progression-free survival (PFS). We used modified Response Evaluation Criteria in Solid Tumors (mRECIST) to assess response to treatment and the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 to evaluate the grading of treatment related toxicity.

Results: The majority of our patients were males (74%), white (47%), 66% of patients had underlying liver cirrhosis, 26% had vascular invasion, and 26% had hepatic disease.

Conclusion: This is the first prospective study to evaluate sorafenib followed by Y90 in HCC. Our study included patients with metastatic HCC and showed that combined use of sorafenib and Y90 was tolerable and was associated with longer OS and PFS compared to previous studies which evaluated sorafenib alone. However, future randomized phase III studies are warranted to assess sorafenib/Y90 in metastatic disease setting.

Clinical trial identification: NCT01990002

Legal entity responsible for the study: MD Anderson Cancer Center

Funding: Bayer Pharmaceuticals Company

Disclosure: All authors have declared no conflicts of interest.

Assessing cancer risk in patients with HFE gene variants and type 1 hereditary hemochromatosis

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Background: Patients with type 1 hereditary hemochromatosis (HH) are reported to have a 20-200-fold increased risk of hepatocellular carcinoma. However, not much is known about the risk of developing non-hepatobiliary cancers in these patients or those heterozygous for HFE variants. The purpose of this study is to assess the risk of non-hepatobiliary cancers in a large cohort.

Methods: Using the Geisinger-Regenstrief DiscoveEHarr cohort, we sequenced whole exomes of 51,289 study participants to further analyze the HFE gene variations (C282Y, H63D or 565C) for cancer development. The cancer prevalence and statistical significance was assessed in both genders from multiple HFE genotypes.

Results: There were 51, 270 participants in this study: 30, 280 (59%) women and 20, 990 (41%) men. There was an increased risk of cancer overall among patients who harbored one or more HFE gene mutation (Kruskal-Wallis; p < 0.0001). While most cancers occurred in patients who had no known HFE mutations (20.5%), cancers were found in patients heterozygous for H63D/WT (6.14%) and C282Y/WT (2.31%). When the probability of cancer among men without HFE mutations were compared to other men with varying mutant genotypes, men with one or more HFE mutations had an increased probability of cancer if homozygous C282Y (p = 0.001), compound heterozygous for C282Y/H63D (p = 0.0013), homozygous H63D (p = 0.0011), 565C/WT (p = 0.001). C282Y/565C (p = 0.0011), WTC/C282Y (p = 0.0053) and not H63D/WT mutation (p < 0.1). Among women, H63D/565C and H63D/H63D mutation(s) were associated with an increased risk of cancer (p < 0.0001).

Conclusions: To our knowledge, this is the first whole exome sequencing study analyzing the HFE gene variants for cancer risk in over 50 thousand individuals. This study showed that cancer risk is increased in both HFE variants and non-HFE variants carriers and that cancer screening should be considered in this cohort.

Legal entity responsible for the study: Geisinger Medical Center and Regenstrief Pharmaceuticals

Funding: Regenstrief Pharmaceuticals

Effect of adjuvant chemotherapy and chemoradiotherapy in patients with ampullary carcinoma: A NCDB analysis

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Background: Ampullary carcinoma is a rare gastrointestinal cancer and the benefit of adjuvant chemotherapy is debatable. We used the National Cancer Data Base (NCDB) to evaluate if adjuvant chemotherapy (AC) or adjuvant chemoradiation (ACR) provides a survival benefit in patients undergoing resection.

Methods: Utilizing the NCDB from 2004-2012, 3949 patients who underwent ampullary tumor resection were identified. All patients had confirmed histological diagnosis, and follow up. Patients not considered candidates for AC or ACR were excluded. 2194 patients underwent surgical resection alone (S). This cohort was compared with 874 patients who received AC, and 1128 patients ACR. Patients were stratified into node negative (NN) or node positive (NP) (NN) disease. Overall survival (OS) was performed utilizing Kaplan-Meier method, and log-rank tests were used for statistical comparisons. Cox proportional hazards were performed to control for age, gender, race, type of facility (academic versus non-academic), income, education, Charlson-Deyo score (CDS), T stage, and histologic grade. All tests were two sided and a P value of < 0.05 was considered significant.

Results: The median age at diagnosis was 65 years (range 20-90). In the NN group, median OS was not reached (NR) for AC, NR for ACR and 101 months (mo) for S (p = 0.21). In contrast in the NP group, median OS was 33 mo for AC, 35 mo for ACR.
and 27 mo for S (p < 0.0001). In a multi-variate analysis of NP patients, AC or ACR were independent positive prognostic factors with Hazard Ratio 0.79 for AC (95% CI 0.68-0.9, p = 0.0085) and 0.76 for ACR (95% CI 0.67-0.8; p < 0.0001) when compared to S. No differences were seen when AC was directly compared to ACR. Older age, tumor size larger than 2 cm, poor histological grade, high CJD, low income and black race were independent negative prognostic factors.

Conclusions: Adjuvant chemotherapy or chemoradiotherapy are associated with a significant survival benefit in patients with resected node positive ampullary carcinoma when compared to surgery alone. The addition of radiation, however, does not confer additional benefit over adjuvant chemotherapy. Patients with node negative disease do not seem to benefit from adjuvant therapy regardless of primary tumor size.

Legal entity responsible for the study: Mayo Clinic

Funding: None

Disclosure: All authors have declared no conflicts of interest.

714P Gemcitabine and platinum-based chemotherapy in first line treatment of hepatocellular carcinoma: AN AGEO multicenter retrospective study

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Background: Hepatocellular carcinoma (cHCC-ICC) is a rare primary hepatic tumor combining features of cholangiocarcinoma (ICC) and hepatocellular carcinoma (HCC). The aim was to evaluate the overall survival (OS), progression free survival (PFS) and prognostic factors in unresectable cHCC-ICC treated by gemcitabine (gem) and platinum-based chemotherapy in first line systemic treatment.

Methods: Data from patients treated for advanced cHCC-ICC by gem and platinum-based chemotherapy in six French university hospitals between 2008 and 2016, were retrospectively collected. The diagnosis of cHCC-ICC was based on histological analysis or, in case of typical histology of ICC or HCC, on discordant CT-Scan findings and/or tumor marker (alpha-fetoprotein, carbohydrate antigen 19-9, carcinomembrynic anti- gen) serum levels suggesting the alternative histology. OS and PFS were estimated by Kaplan-Meier method. Prognostic factors were analyzed by Log-rank test in univariate analysis and by Cox model in multivariate analysis. Statistical analysis was performed using Graph Pad Prism 6.

Results: Forty patients were included (79% men, median age 66 years [extremes 52- 88]). cHCC-ICC was histologically proven in 55% of cases. At diagnosis, twenty-three patients (57.5%) had metastatic synchronous lesion. Twenty-nine patients (72.5%) were treated by gem + oxalaplatin (GEMOX), 9(22.5%) by GEMOX + bevacizumab, 2(5%) by gem + cisplatin. Eighteen patients (45%) received second line of treatment. In the first line, patients received a median of 10 cycles of chemotherapy (extremes 1- 28). RECIST1.1 criteria were reported in 35 cases. 9 patients (25.7%) had partial response, 18 (51.4%) had stable disease, 8 (22.8%) had tumor progression at first evaluation. Median PFS and OS were 9 and 15.4 months, respectively. In multivariate analysis, significant prognostic factors of poor OS were: positive serology for hepatitis B virus and/or C (HR = 1.35 [95% CI 1.13-1.34] p = 0.031), serum bilirubin level > 20 umol/L (HR = 1.66 [95% CI 1.57-17.54] p = 0.007), ECOG score > 2 (HR = 2.46 [95% CI 1.23-61.75] p = 0.004).

Conclusions: These data suggest a chemosensitivity of cHCC-ICC to gemcitabine and platinum based chemotherapy.

Legal entity responsible for the study: Dr. Yann Touchefeu

Funding: None

Disclosure: All authors have declared no conflicts of interest.
The nationwide cancer genome screening project in Japan, SCRUM-Japan GI-screen: Efficient identification of cancer genome alterations in advanced biliary tract cancer


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Background: We have conducted the Nationwide Cancer Genome Screening Project in Japan since April 2015 using Next Generation Sequencing in cancers of digestive system, called as the SCRUM-Japan GI-GS CIE. We evaluated the frequency of cancer genome alterations. We show the result of advanced biliary tract cancer cohort (aBTC; intra hepatic bile duct (IHB), extra hepatic bile duct (EHBD), gallbladder (GB), and ampulla of Vater (AV)).

Methods: This study is ongoing with the participation of 20 major cancer centers. Patients who plan to or receive systemic chemotherapy were eligible. DNA and RNA were extracted from FFPE tumor samples and were analyzed by the Oncomine Cancer Research Panel (OCR) which allows to detect gene mutation, copy number variant (CNV) and fusions across 143 genes in a CLIA certified CAP accredited laboratory. The detected genomic variants data were classified according to genetic drivers of cancer including gain- and loss-of-function or single nucleotide variant based on the Oncomine Knowledgebase.

Results: As of October 31st in 2016, a total of 109 aBTC samples were analyzed and the sequence with the OCR was successfully performed in 73 (67.6%). The frequent/important mutations in 73 samples of which results were available were shown in table 1.

Table: 716P

<table>
<thead>
<tr>
<th>Gene</th>
<th>IHB (n=51)</th>
<th>EHBD (n=27)</th>
<th>GB (n=10)</th>
<th>AV (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAF</td>
<td>10(32)</td>
<td>8(26)</td>
<td>2(20)</td>
<td>0</td>
</tr>
<tr>
<td>TP53</td>
<td>6(19)</td>
<td>5(19)</td>
<td>6(60)</td>
<td>2(20)</td>
</tr>
<tr>
<td>BRF1</td>
<td>1(3)</td>
<td>1(3)</td>
<td>1(10)</td>
<td>0</td>
</tr>
<tr>
<td>PKCɛA</td>
<td>0</td>
<td>0</td>
<td>4(40)</td>
<td>0</td>
</tr>
<tr>
<td>BRCA2</td>
<td>0</td>
<td>2(6)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ATM</td>
<td>1(3)</td>
<td>2(6)</td>
<td>1(10)</td>
<td>0</td>
</tr>
<tr>
<td>IDH1</td>
<td>3(10)</td>
<td>1(3)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>FGF2R2/3</td>
<td>2(6)</td>
<td>0</td>
<td>0</td>
<td>1(20)</td>
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<tr>
<td>ERRBB3</td>
<td>1(3)</td>
<td>3(10)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Conclusions: This nationwide screening system is efficient to detect rare gene alterations in aBTC. This novel knowledge provides an intriguing background to investigate new target approaches and represents a progress toward more precision medicine.

Clinical trial identification: UMIN00016344

Legal entity responsible for the study: SCRUM-Japan GI-GS CIE.


S. Nomura: Employment: Asahi Kasei An Immediate Family Member. K. Shitara: Advisory Role: Chugai Pharma, Takeda, Bayer, Lilly. Honoraria: Bristol-Myers Squibb, etc. Research Funding: Dainippon Sumitomo Pharma, MSD, Sanofi, Daiichi Sankyo, Taisho Pharmaceutical, etc. A. Ohtsu: Employment: Celgene An Immediate Family Member. Research Funding: Bristol-Myers Squibb, T. Yoshino: Research Funding: GlaxoSmithKline, K.K. Boehringer Ingelheim GmbH. All other authors have declared no conflicts of interest.

Prognostic implication of inflammation-based prognostic scores in patients with intrahepatic cholangiocarcinoma (iCCA) treated with first-line Gemcitabine plus Cisplatin (GEMCIS)


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Background: There is increasing evidence that inflammation-based prognostic scores have prognostic value in several cancer types, including iCCA. However, most of the studies are focused on evaluating their value in patients with resectable disease. We retrospectively evaluated the prognostic implication of inflammation-based prognostic scores including modified Glasgow Prognostic Score (mGPS), Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Methods: Between April 2010 and May 2015, a total of 296 patients with histologically documented advanced iCCA were treated with first-line GEMCIS in Asan Medical Center, Seoul, Korea. Of these, 257 patients had complete data for inflammation-based prognostic scores and were included in this study. Primary endpoint was overall survival (OS).

Results: Median age was 59 years (range, 27-78) and 158 patients (61.5%) were male. Initially metastatic disease was the most common disease status at GEMCIS (n = 170, 66.1%) followed by recurrence after surgery (n = 44, 17.1%) and locally advanced unresectable disease (n = 43, 16.7%). With a median follow up duration of 25.9 months (95% CI, 19.6-30.4 months), median OS was 9.1 months (95% CI, 8.0-10.2 months). In univariate analyses, high mGPS and NLR scores were associated with poorer OS (mGPS 1-2 vs 0: median 6.9 vs 14.1 months, p < 0.01; and NLR 1-2 vs 0: 6.9 vs 11.8 months, p < 0.01). PLR was not associated with OS (p > 0.39). In the multivariate analysis including potential prognostic factors such as disease extent, number of metastatic sites, performance status and liver cirrhosis, only high mGPS remained significant (1-2 vs 0; HR = 1.59, p < 0.01). Conclusions: The current study suggests that mGPS might be the relevant prognostic index which can stratify the survival outcomes of patients with unresectable or metastatic iCCA who received first-line GEMCIS.

Legal entity responsible for the study: Asan Medical Center, University of Ulsan College of Medicine.

Funding: None

Disclosures: All authors have declared no conflicts of interest.

Phase 2 study of triplet chemotherapy with oxaliplatin, irinotecan and S-1 (OIS) as first-line treatment in patients with advanced biliary tract cancer (BTC)

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Background: Although gemcitabine plus cisplatin has been established as the standard first-line chemotherapy for patients with advanced BTC based on the success of the ABC-02 trial, the overall prognosis is still poor as median survival of less than 1 year. Therefore, we investigated novel combination of three drugs including oxaliplatin, irinotecan and S-1, oral fluoropyrimidine, (OIS) for advanced BTC.

Phase 2 study of triplet chemotherapy with oxaliplatin, irinotecan and S-1 (OIS) as first-line treatment in patients with advanced biliary tract cancer (BTC)
Methods: Chemotherapy-naive patients with histologically documented unresectable or metastatic BTC were eligible for this study. Patients received oxaliplatin 65 mg/m² Day 1, 5-fluorouracil 135 mg/m² Day 1, and 5-fluorouracil 460 mg/m² BID Day 1-7, every 2 weeks, until the disease progression or intolerable toxicities. Primary endpoint was objective response rate (ORR) defined by RECIST v1.1 and secondary endpoints include progression-free survival (PFS), overall survival (OS) and safety profile. According to the Simon’s optimal two-stage design with type I error of 0.05 and a power of 80%, 31 patients were needed with a hypothesis of improving ORR from 20% to 35%. Results: Between October 2015 and June 2016, a total of 32 patients were enrolled in two referral institutes in Korea. Median age was 64 years (range 40-76) and 24 (75%) patients were male. All but one patient (97%) had metastatic or recurrent disease. Intrahepatic lesion is the most common primary tumor site (n = 13, 41%) and followed by gallbladder (n = 11, 34%) and extrahepatic lesion (n = 8, 25%). With median follow-up duration of 10.1 months, patients received median 12 cycles (range, 1-21) of treatment. ORR was 50% as partial response was achieved in 16 patients. Median PFS was 7.1 months (95% CI, 5.3-8.8) and median OS was not reached. The 1-year PFS and OS rates were 25% and 59%, respectively. Most common grade 3-4 adverse events were neutropenia (n = 10, 32%), followed by diarrhea (n = 2, 6%) and peripheral neuropathy (n = 2, 6%). Conclusions: OIS triplet combination chemotherapy was feasible and showed promising efficacy outcomes as first-line treatment in patients with advanced BTC. Randomized trial is needed to validate the efficacy of this triplet regimen.

Clinical trial identification: NCT02527824

Legal entity responsible for the study: Hallym University Medical Center and Asan Medical Center

Funding: None

Disclosure: All authors have declared no conflicts of interest.

721P Prognostic impact of hepatitis B virus (HBV) infection in advanced intrahepatic cholangiocarcinoma (iCCA) patients (pts) treated with first-line gemcitabine plus cisplatin (GEMCIS)

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Background: HBV infection is a well-known risk factor of iCCA. However, its prognostic impact has rarely been investigated in pts with advanced iCCA who received chemotherapy.

Methods: Between April 2010 and May 2015, a total of 296 pts with histologically documented advanced iCCA received first-line GEMCIS in Asan Medical Center, Seoul, Korea, and were included in this retrospective analysis. Primary endpoint was overall survival (OS). In the multivariate analysis, variables which showed potential association with survival (p < 0.15) in the univariate analysis were included.

Results: Median age was 59 years (range, 27-78), and 62 (20.9%) pts with hepatitis B surface antigen positive formed the HBV group. Initially metastatic disease was the most common disease status at the time of GEMCIS (n = 184, 62.2%) followed by recurrence after curative surgery (n = 69, 23.3%) and locally advanced unresectable disease (n = 43, 14.5%). In comparison with the non-HBV group, HBV group were related with young age (mean 56.4 vs 60.0), male predominance (74.2% vs 57.3%), lower rates of elevated CA 19-9 (42.9% vs 68.5%) and alkaline phosphatase (42.6% vs 60.5%) (p < 0.05 for all). In univariate analysis, HBV infection showed marginal relationship with poor OS (vs non-HBV infection; median 8.3 vs 10.0 months; HR 1.50; 95% CI, 0.75-3.00; P = 0.21). In multivariate analysis including potential prognostic factors, however, HBV group was significantly associated with poorer OS (HR = 1.52; 95% CI, 1.02-2.20). In addition, initially metastatic disease (vs locally advanced/recurrent disease; HR = 1.49), number of metastatic sites ≥2 (vs 0-1; HR = 1.50), poor ECOG performance status (2 vs 0-1; HR = 1.94), elevated total bilirubin (vs normal; HR = 1.83), and albumin < 3.5 g/dL (vs ≥ 3.5 g/dL; HR = 1.53) were significantly associated with poorer OS (P < 0.05 for all).

Conclusions: Our results suggest that HBV infection might be an independent poor prognostic factor in pts with advanced iCCA treated with first-line GEMCIS. Further translational research is needed to define the differences in the molecular phenotypes between HBV- and non-HBV-associated iCCA.

Legal entity responsible for the study: Asan Medical Center, University of Ulsan College of Medicine

Funding: None

Disclosure: All authors have declared no conflicts of interest.

720P Inoperable carcinoma gallbladder: Comparison of two palliative chemotherapy regimens (gemcitabine-platinum versus CAPEOX)

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Background: Cancer of the gallbladder (CaGB) constitutes one of the ten commonest cancers in women in north India. Palliative chemotherapy is indicated for the advanced stage, inoperable patient in good performance status (PS). There is no standard-of-care regimen for this disease. We prospectively evaluated the efficacy & safety of GEMPLAT vis-à-vis CAPEOX chemotherapy in this cohort of patients.

Methods: Fifty chemo-naive, newly diagnosed patients (25 in each arm) of inoperable CaGB, in good PS (0, 1, II) were included. Patients were randomised to receive either GEMPLAT or CAPEOX. Primary end point was response rate (RR) & progression free survival (PFS); secondary end point: Overall survival (OS), toxicity & quality of life (QOL). Response assessment was done after every two cycles using the RECIST 1.1 criteria. QOL was assessed every two cycles.

Results: Thirty one females & 19 males, mean age of 45.7 years (range 32 to 69) were included. There were no CRs in either arm. Partial response (PR) & stable disease (SD) was seen in 6 (24%) & 8 (32%) patients, respectively, in GEMPLAT arm; and 2 (8%) and 5 (20%) achieved PR and SD, respectively in CAPEOX group. Overall response rate (ORR) was 24% vs 8%, respectively, for GEMPLAT & CAPEOX. The median OS in GEMPLAT arm was 9.9 months versus 2.6 months in CAPEOX. The median PFS was higher in GEMPLAT group (7.6 months) as compared to CAPEOX group (1.5 months). Grade 3/4 anemia & neutropenia occurred in 3 (12%) & 2 (8%) patients in the GEMPLAT arm, respectively with no grade 3/4 hematological toxicity in the CAPEOX arm. Five (20%) patients developed grade 3/4 transaminisits on GEMPLAT. One (4%) patients in CAPEOX arm developed sensory neuropathy and 3 (12%) have grade 3/4 skin toxicity.

Conclusions: In our study, the GEMPLAT regimen showed higher RR, OS and PFS as compared to CAPOX. QOL was better in the GEMPLAT arm. CAPOX regimen was better tolerated and less toxic. The main toxicity of GEMPLAT was haematological & hepatic while that of CAPOX was dermatological. We conclude that GEMPLAT should be the standard-of-care first line palliative chemotherapy regimen for inoperable CaGB patients in good PS. Larger, multi-centre studies are needed to confirm our findings and to compare CAPOX/other regimens with GEMPLAT.

Legal entity responsible for the study: Prof. Dr. Hemant Malhotra

Funding: None

Disclosure: All authors have declared no conflicts of interest.
A phase 2 study of lenvatinib monotherapy as second-line treatment in unresectable biliary tract cancer: Primary analysis results


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Background: Lenvatinib (LEN) inhibits vascular endothelial growth factor receptors, fibroblast growth factor receptors, and platelet-derived growth factor receptor-a. These targets have been shown to be expressed in patients (pts) with biliary tract cancer (BTC). A planned interim analysis of this phase 2 study demonstrated preliminary efficacy of LEN 24 mg/d in pts with BTC.

Methods: This open-label phase 2 study conducted in Japan enrolled pts aged ≥20 years with a confirmed unresectable BTC, measurable disease per Response Evaluation Criteria in Solid Tumors v1.1, and 1 prior gemcitabine (GEM)-based doublet chemotherapy to receive LEN 24 mg/d. The primary endpoint was objective response rate (ORR). Secondary objectives included disease control rate (DCR), overall survival (OS), progression-free survival (PFS), safety, and pharmacokinetics.

Results: The primary analysis was performed with data on 26 pts. Median age was 64 years and 15 pts (58%) were men. Eastern Cooperative Oncology Group performance status was 0 for 19 pts (73%) and 1 for 7 pts (27%). Six pts (23%) had prior surgery, 20 pts (77%) received prior GEM + nab-paclitaxel, and 6 pts (23%) received prior GEM. TN 1. There were 6 pts (23%) with intrahepatic bile duct; 8 (31%) with extrahepatic bile duct, 10 (39%) with gallbladder, and 2 (8%) with ampulla of Vater primary tumor locations. ORR was 12% (90% CI: 3.2–27.2%) by both independent and investigator review. DCR was 83% (90% CI: 68.2–94.6%) by investigator, and 46% (90% CI: 29.2–63.8%) by independent review. Median PFS was 3.2 months (95% CI, 2.8–7.2) and 1.6 months (95% CI, 1.4–3.2) by investigator and independent review, respectively. Median OS was 7.4 months (95% CI, 4.5–11.3). All pts had treatment-emergent adverse events (TEAEs). Common TEAEs included hypertension, dyspnoea, proteinuria, palmar-plantar erythrodysesthesia, decreased appetite, thrombocytopenia, and fatigue. TEAEs led to dose reduction in 21 pts (77%) and discontinuation in 2 pts (8%).

Conclusions: LEN 24 mg/d showed anti-tumor activity in pts with unresectable BTC who had failed GEM-based combination therapy. Toxicities were manageable with dose modifications, reductions, or discontinuations.

Clinical trial identification: NCT023979616

Legal entity responsible for the study: Eisai Inc

Funding: Eisai Inc


A phase 2 study of lenvatinib monotherapy as second-line treatment in unresectable biliary tract cancer: Primary analysis results

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Background: Cholangiocarcinoma (CC), gallbladder cancer (GBC) and ampullary cancer (AC) (collectively BTCs) are poor-prognosis cancers. Cisplatin-gemcitabine chemotherapy is the standard treatment for patients (pts) with advanced BTC. New treatment targets are warranted; the human epidermal growth factor receptor (HER)-2 and HER-3 are treatment targets in BTC; treatment targeting this pathway may warrant evaluation.

Methods: Pts diagnosed with BTC and available paraffin-embedded archival tissue were eligible. Seventy consecutive pts were required (power 0.91; assumptions: 5% outcome rate, 0.1 difference in rate). Eligibility criteria in Solid Tumors v1.1, and 1 prior gemcitabine (GEM)-based doublet chemotherapy were used. Clinical characteristics included: stage at diagnosis (I/II vs. III/IV), age (<65 vs. ≥65), histology (mixed vs. pure), HER overexpression was identified in 77% of pts diagnosed with BTC; treatment targeting this pathway may warrant evaluation.

Results: Of 167 screened pts between Jan-13 and Jul-15, 76 samples were retrieved for quality assessment; 67 were eligible with a median age of 65.6 years (range 22.9-79.3); 51.2% were female; 85% had ECOG performance status 0-1; all were adenocarcinomas. Primary site was GBC (n = 10, 14.9%), CC (n = 44, 65.7%; n = 26 intra-hepatic (IHC), n = 18 extra-hepatic (EHC) and AC (n = 13, 19.4%). Stage at diagnosis: I/II (n = 21, 31.3%) or III/IV (n = 46, 68.7%). Estimated median overall survival (OS) for all pts was 15.9 months (95% CI 11.1–20.3). HER-2 overexpression was identified in 1 pt (15%). HER-3 overexpression was identified in 16 (23.9%). A 1 pt was classified as "3+" positive by IHC and 15 were confirmed by FISH following a "2+" expression in IHC. Neither HER-2 (p = 0.103) nor HER-3 (p = 0.087) impacted on OS. No factors related to HER-3 overexpression were identified.

Conclusions: HER-3 is overexpressed in a significant subset of pts diagnosed with BTC; treatment targeting this pathway may warrant evaluation.

Legal entity responsible for the study: MCRC Biobank

Funding: Dr Lamarca was part-funded by Pancreatic Cancer Research Fund (PCRF) Grant and Spanish Society of Medical Oncology (SEOM) Fellowship Grant. Dr Gaidy was part-funded by “Clinical Unit Visit” European Society of Medical Oncology (ESMO) Fellowship.

Disclosure: All authors have declared no conflicts of interest.
Actionable molecular alterations in advanced biliary tract carcinomas: Preliminary data from the ProfiLER program (NCT01774409)

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Background: Patients (pts) with advanced biliary tract cancers (BTC) have poor prognosis and limited therapeutic option. The objectives were to characterize tumor genomic alterations for patients diagnosed with BTC enrolled in the ProfiLER program and identify actionable targets.

Methods: The ProfiLER program is a multicentric prospective molecular profiling trial in patients with advanced cancers. DNA extracted from archival or freshly collected tumor samples was analyzed by targeted exon sequencing (NGS) of 59 cancer related genes and whole genome array comparative genomic hybridization (CGH). Genomic profiles were discussed at a dedicated molecular tumor board (MTB) for recommendation of molecularly targeted agents (MTAs) when applicable.

Results: Of 2184 included pts in the ProfiLER program, 45 pts diagnosed with advanced BTC (intrahepatic cholangiocarcinoma – ICC, n = 32; vascular carcinoma, n = 7; main biliary duct, n = 5) were included between March 2013 to April 2017. Median age was 61 (range 37-79) years, and 21 pts (47%) were women. The median time from inclusion to MTB discussion was 12 (range 3-98) weeks. NGS was feasible for 31 pts (69%) and CGH for 24 (53%), both analyses were available for 22 (49%) and at least one analysis was available for 34 (75%) pts. 19 pts (56% of 34 analyzed pts) had at least one actionable alteration: CDKN2A homozygous deletion (n = 8), MDM2 amplification (n = 5) and PDKFrA amplification (n = 5) were recurrent alterations. Among 31 pts with NGS data, 7 had TP53 mutations, 4 had KRAS mutations while none had BRAF mutations. Four pts received MTA based on the alteration identified (CDK4 inhibitor for CDK4 deletion, ERBB2 inhibitor for an ERBB2 amplification, EGFR inhibitor for EGFR mutation and mTOR inhibitor for homozygous TSC2 deletion), progressive disease was the best response in all pts.

Conclusions: CGH and NGS identified actionable alterations in 56% of pts with BTC for whom analyses could be performed. However, the analyses were both feasible in only 49% of patients due to the use of archival biopsy samples in most cases.

Precision medicine for patients with advanced biliary tract cancers: Updated results from the prospective MOSCATO trial

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Background: Advanced biliary tract cancers (BTCs) are heterogeneous diseases with a median overall survival (OS) < 1 year. Platinum-based chemotherapy doublets are the frontline standard-of-care. Increasing evidence points out the strong addiction of BTCs to molecular alterations. The objective of this study was to evaluate the clinical relevance of actionable alterations as a tool to guide patients to an appropriate clinical trial or personalized treatment.

Methods: Patients from AGEO/FRENCH groups were reviewed in this retrospective study. Following analysis, 25 patients could be orientated to an appropriate early clinical trial or accurate MTA (25/38, 66%), and 19 patients could be treated on the basis of molecular alterations (19/38, 50%). For the biologic-driven treatment group, The PFS ratio was 1.52 [0.88, 7.1]. Six patients (32%) had an objective response (complete or partial) (PR) response, 16 (84%) had a clinical benefit (stable disease – PR + CR), and 7 (37%) had a PFS of 6 months. This strategy led to a significant overall survival improvement compared to patients who were not treated according to their tumor molecular characteristics (HR = 0.26 [95%CI, 0.10 – 0.67], p = 0.001).

Conclusions: With 25 patients out of 48 included (52%) driven to a MTA, patients with BTCs are ideal candidates for molecular profiling.

Preoperative chemoradiotherapy after induction FOLIRINOX improves R0 resection margins rate and histological response in patients secondary resected in borderline or locally advanced pancreatic adenocarcinoma

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Intratumoral heterogeneity of SMAD4 immunohistochemical (IHC) expression and its role in prediction of recurrence patterns in patients with resectable pancreatic cancer (PC)

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Background: Up to 30% of patients with resectable PC have only locoregional recurrences and never experience metastatic disease. Several authors reported SMAD expression can predict locoregional pattern of PC progression. The aim of our study was to evaluate consistency of SMAD4 expression in different tumor areas and its correlation with patterns of PC recurrence.

Methods: Records of PC patients treated in N. N. Blokhin Russian Cancer Research Center since 2002 to 2015 were analyzed. Inclusion criteria for this retrospective analysis were: non-metastatically morphologically confirmed PC, R0-R1 resection and archived tumor samples availability. Formalin-fixed, paraffin-embedded tissue sections of different areas of the primary tumor (central area and zones of invasion) and of lymph node metastases were analyzed via IHC for SMAD4 expression using TMA technology.

Results: A total of 336 tissue sections obtained from 91 patients were assessed for SMAD4 expression. Positive SMAD4 expression was revealed in tumor blocks of 26 patients. There was high intratumoral heterogeneity of SMAD4 expression: only in 4 of 26 patients (15.4%) SMAD4 expression was positive in all assessed tumor slides. There were 54 recurrences (9 locoregional, 41 distant and 4 both local and distant) with median follow-up 21.7 months. There were no correlation between SMAD4 expression and locoregional recurrence pattern (Goodman & Kruskal’s tau coefficient 0.08 ± 0.03, p = 0.15). There was no difference in distant recurrence-free survival by SMAD4 IHC expression status: medians were 11.8, 19.5 and 7.1 months for patients with SMAD4 negative, heterogeneous or positive tumors, respectively (p = 0.987). SMAD4 status also showed no prognostic significance: medians overall survival were 20.5, 32.6 and 15.2 months for patients with SMAD4-positive, heterogeneous and negative tumors, respectively (p = 0.331).

Conclusions: Different areas inside the primary tumor and lymph node metastases heterogeneous express SMAD4. SMAD4 IHC expression is not a biomarker of a recurrence pattern following surgical resection for PC.

Outcome of patients with pancreatic adenocarcinoma with complete pathological response following neo-adjuvant therapy

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Background: Recently, the natural history of metastatic pancreatic adenocarcinoma (PC) has changed after the introduction of new chemotherapeutic regimens.

Results: A total of 101 pts received TX, and 75% (76/101) pts had a baseline and ≥1 postbaseline QoL assessment. The median age was 65 years (range, 42-85); 53% had an ECOG PS 0-1. All QoL dimensions were improved/stable in 60% of pts (Table). In general, median time to improvement was ≤1 week of completing the first TX (28 days/ C). A majority (>60%) of pts had ≥1 complete resolution of anxiety (tense), constipation, depression, nausea, or pain during induction. Forty-two percent of pts received additional TX during the IC phase.

Conclusions: QoL was generally improved/stable during induction, with some dimensions improving within 1 week of completing the first C. This suggests that QoL is
preserved or improved with nab-P + G and indicates that the regimen was active and tolerable, with a majority of pts completing induction without PD. NCT02301143.

Clinical trial identification: NCT02301143

Legal entity responsible for the study: Celgene Corporation

Disclosure: P.A. Philip: Research funding: Celgene, Bayer, Incyte; consultant or advisory role: Celgene, speaker’s bureau: Bayer, Roche, Sanofi, Amgen. P. Hammel: Consultant or advisory role, honoraria, and travel accommodations, expenses: Celgene. E.S. Kim: Honoraria, advisory role, speaker’s bureau: Amgen, Celgene, Lilly, Roche. A. Zakari: Speaker’s bureau: Amgen, Celgene. C. Borg, J. Lacy: Consultant or advisory role, honoraria, and travel accommodations, expenses: Celgene. E.S. Kim: Consultant or advisory role: Celgene; speaker’s bureau: Bayer, Roche, Sanofi, Amgen. Lilly, Roche, Amgen. Merck-Serono, MSD, Sanofi, Lilly; speaker’s bureau: Celgene, Bayer, Roche, Sanofi, Amgen, Lilly. J. Shiansong Li, T.J. Ong, T. Nydam: Employment, stock ownership, Celgene. All other authors have declared no conflicts of interest.

731P Prognosis of familial pancreatic cancer (FPC): A matched case analysis

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Background: FPC is a putative genetically heterogeneous syndrome defined as kindreds with multiple blood relatives with pancreatic adenocarcinoma (PDAC). It has been hypothesized that germline mutations in DNA repair genes contribute to FPC, resulting in variable outcomes and response. We evaluated survival in FPC patients (pts) with resectable and unresectable PDAC.

Methods: Pts were identified from the Ontario Pancreatic Cancer Study database, recruited from January 1998–July 2016. All pts were seen by genetic services. FPC pts were age and stage matched with cases without a family history of PDAC and who tested germline BRCA mutation negative (non-FPC). Stage was classified as early operable (I/II) or late inoperable (III/IV). Pts were matched within 5 years of the treatment period. Only those who had either received surgery or at least 1 cycle of chemotherapy were included. The Kaplan-Meier method was used to assess survival.

Results: 144 pts were evaluated, 72 in each cohort. In the FPC group, 65 pts had at least 1 FDR with PDAC and 7 pts, at least 2 relatives (1st-3rd degree) with PDAC. Median age was 66 years; there were more females in the FPC group (54% vs 49%), 33 pts (46%) in each group had early stage disease and received surgery. Adjuvant therapy was given in 70% and 73% of the FPC and non-FPC cohorts respectively. 1 FPC pt, received adjuvant gemcitabine/erbolinib. 6 non-FPC pts received FOLFIRINOX, 3 as neo-adjuvant and 3 as adjuvant treatment. Of those with late stage disease, (n = 39 each), combination chemotherapy was given in 23 (59%) and 28 (72%) pts in FPC vs non-FPC groups respectively. The median overall survival (OS) was 16 months (mths) in the FPC group vs 13mths in the non-FPC group (p = 0.46). Stratifying by stage, in FPC vs non-FPC pts, median OS in early disease was 31 vs 27 mths (p = 0.73) and in late disease 13 vs 9 mths (p = 0.12). Platinum was used in 18 (46%) FPC and 17 (44%) non-FPC pts with late disease. Platinum regimens improved median OS overall compared to no platinum (12mths vs 9mths, p = 0.04) but was not associated with FPC status.

Conclusions: FPC is poorly understood but trends towards a better prognosis and response to therapy. The use of platinum based chemotherapy in these pts could be considered; however further research is warranted.

Legal entity responsible for the study: Steve Gallinger

Disclosure: All authors have declared no conflicts of interest.
Background: BRCA1/2 mutation carriers have an increased risk for breast cancer (BC), ovarian cancer (OC), prostate cancer and pancreatic cancer (PC). On this basis, the NCCN Guidelines classified according to the Modena Criteria did not increase the BRCA mutation detection rate. Notably, PC in families with PC associated to BC and/or OC. The NCCN Guidelines compared to our retrospective study confirms the high rate of positive BRCA1/2 test detections (detection rate 21.3%). Mean age at PC diagnosis was lower in patients with family history or BC and/or OC (65.8 years) and in BRCA mutated families (65.7 years) than in general population (72 years). One-year OS rate was higher in patients with family history of BC and/or OC (41.3%) and in BRCA mutated families (59%) than in general population (23%). 5-year OS was around 8% for patients with family history or BRCA mutation in the family and general population.

Conclusions: Our retrospective study confirms the high rate of positive BRCA1/2 test in families with PC, associated to BC and/or OC. The NCCN Guidelines compared to the Modena Criteria did not increase the BRCA mutation detection rate. Notably, PC diagnosed in families with history of BC and/or OC or BRCA mutation showed younger age at diagnosis and better one-year OS. We are planning to test all the remaining families selected by NCCN guidelines.

Legal entity responsible for the study: Dr. Laura Cortesi

Funding: None

Disclosure: All authors have declared no conflicts of interest.

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Table: 73SP

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<th>Multivariate Analysis (DFS)</th>
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<td>CD 8 High vs. Low (Reference)</td>
<td>0.002</td>
<td>0.366 (0.146-0.858)</td>
<td>0.695 (0.270-2.919)</td>
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<td>CD/CD 8 ratio High vs. Low (Reference)</td>
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<td>0.393 (0.141-0.983)</td>
<td>0.112 (0.344-0.884-1.281)</td>
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<td>CD 68/CD 4 ratio High vs. Low (Reference)</td>
<td>0.085</td>
<td>0.424 (0.123-1.114)</td>
<td>0.261 (0.135-1.561)</td>
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Randomized phase 2 trial of peri- or post-operative chemotherapy in resectable pancreatic adenocarcinoma

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Background: Pancreatic ductal adenocarcinoma (PDAC) has a remarkable trend to metastasize early. Accordingly, there is a strong rational to investigate preoperative chemotherapy in patients with resectable disease. We conducted a multicenter randomized phase 2 trial (PACT-15; NCT01196030) to assess the role of combination chemotherapy in perioperative setting.

Methods: Treatment-naïve patients with 18-75 yr, KPS=60 and pathologically confirmed stage I-2 resectable PDAC were randomized to surgery followed by 6 cycles of adjuvant gemcitabine 1000 mg/m² or 6 cycles of adjuvant gemcitabine 1000 mg/m² and nab-paclitaxel (135 mg/m²) q3w or 6 cycles of neoadjuvant gemcitabine 1000 mg/m² and nab-paclitaxel (135 mg/m²) alternate weeks followed by surgery and 6 cycles of adjuvant gemcitabine 1000 mg/m². The primary endpoint was safety profile and efficacy was secondary endpoint.

Results: Between September 2010 and April 2015, 88 eligible patients were randomized in 9 Italian centers (arm A: 26, B: 30, C: 32). Basal patients and tumor characteristics were well balanced across arms. One-year EFS (A, B, C) was 62/26 (23%), 15/30 (50%), 23/32 (72%). Median EFS was 4.8, 12.4, 18.9 months (A vs C p=0.002). Three-year OS (A,B,C) was 55%, 56%, 54%. Median OS (A,B,C) was 20.4, 25.1, not reached at 33 months (A vs C p=0.022). Pathological results are summarized in the table. Treatment safety profile was good.

Table: 736P Pathological findings

<table>
<thead>
<tr>
<th></th>
<th>A+B</th>
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<tbody>
<tr>
<td>Enrolled</td>
<td>56</td>
<td>32</td>
</tr>
<tr>
<td>T resection</td>
<td>49 (88%)</td>
<td>27 (84%)</td>
</tr>
<tr>
<td>Intraoperative metastases</td>
<td>7/56 (13%)</td>
<td>2/32 (6%)</td>
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<td>Postoperative metastases</td>
<td>10/56 (18%)</td>
<td>3/32 (9%)</td>
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<tr>
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<td>20/49 (59%)</td>
<td>6/27 (22%)</td>
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<tr>
<td>T1</td>
<td>2/49 (4%)</td>
<td>4/15 (27%)</td>
</tr>
<tr>
<td>No</td>
<td>13/49 (27%)</td>
<td>13/27 (48%)</td>
</tr>
<tr>
<td>Ro</td>
<td>16/49 (33%)</td>
<td>15/27 (56%)</td>
</tr>
<tr>
<td>Median size</td>
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<td>2.0 cm</td>
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</table>

Conclusions: Patients receiving perioperative chemotherapy had significant improvement of EFS and OS as compared to those receiving adjuvant treatment. This trial provides the strongest piece of evidence currently available in favor of preoperative chemotherapy in resectable PDAC.

Clinical trial identification: NCT01196030

Legal entity responsible for the study: IRCCS San Raffaele Scientific Institute, Milan, Italy

Funding: IRCCS San Raffaele Scientific Institute, Milan, Italy

Disclosure: M. Renti: Funding from Celgene, Baxalta, Helion, and Merck-Serono; consultant or advisor for Celgene, Baxalta, Merck Serono, Boehringer, Lilly, Pfizer, AstaZeneca, Novocure, Genentech, Halozyme, Novartis. G. Balzarro: Advisory role for Celgene. M. Falconi: Research funding to institution from Novartis. L. Garini: Consulting/advisory role for Roche, Pfizer, GlaxoSmithKline, Synthelabo, Novartis, Sanofi-Aventis, AstraZeneca, Genomic Health, Merck Sharp & Dohme, Boehringer Ingelheim, Tiziana Pharma, Synaffex, Celgene; patents/royalties/intellectual property with Roche. All other authors have declared no conflicts of interest.
including KPS, disease burden, CRP and did not predict for PFS, OS or toxicity. Of 105 tumours evaluable by IHC, 34 had diffuse strong (ds) CD4 staining which predicted for improved PFS with SEQ therapy (HR 0.43, 95% CI 0.20−0.91); this was not evident for other staining patterns or ds CD4 staining for pts on CON therapy. ds CD4 staining trends towards improved OS with SEQ compared with CON therapy (HR 0.73, 95% CI 0.35−1.52).

On disease progression, 34 pts (13 SEQ, 21 CON) received further anti-cancer treatment. Stroma or HENT1 expression did not predict for PFS or OS with SEQ or CON therapy. Tumour stroma staining, but not CD4 or HENT1, was an independent prognostic factor for improved OS (moderate/extensive vs none/very little, HR 0.55, 95% CI 0.37−0.84).

Conclusions: Whole blood CD4A activity was not a useful predictive biomarker, due to the dominant neutrophil effect. Instead, strong tumour CD4A expression predicted for pts most likely to have a survival benefit from SEQ therapy and warrants further exploration.


Legal entity responsible for the study: Cambridge University Hospitals NHS Foundation Trust

Funding: Celgene UK

Disclosure: P. Comic: Funding for the SIEGE clinical trial from Celgene Advisory boards in the last 2 years for BMS, Novartis, MSD, Pierre Fabre, Basalta. J.W. Valle: Speakers’ Bureau, Travel, accommodations and expenses from Celgene. B. Bau: Research funding and provision of trial drug from Celgene. Travel, accommodation and registration expenses for ASCO and ESMO Congresses from Bayer. Consulting and advisory role with Baxter Healthcare, Astex, Celgene.

Methods: To investigate the association between these polymorphisms and toxicities in patients (pts) treated with FOLFIRINOX in the JASPAC 06 study.

Results: Of 399 eligible pts enrolled in JASPAC 06 study, 203 pts were eligible in this analysis. UGT1A1 was reported as wild (W) type (+/+) in 118 pts and heterozygous (H) type (−/+; −/−) in 81 pts. Remaining four pts with homozygote (−/−) or compound heterozygote (−/+; −/−) were excluded because of small population. Among 199 pts, 79 pts were treated with original regimen and 120 pts with modified regimen. In the original FOLFIRINOX group, 54/25 pts were W/H type. The median age was 60 (51−68) years and P50 was 57/52%. Incidences of grade 3/4 leucopenia, neutropenia, febrile neutropenia, diarrhoea, anorexia and grade 4 neutropenia in pts with W/H type were 28/44%, 59/68%, 24/40%, 4/20%, 9/24% and 24/40%, respectively. In the modified FOLFIRINOX group, 64/56 pts were W/H type. The median age was 62.5/62 years and P50 was 70/70%. The same toxicities as above were 22/22%, 44/50%, 57/61%, 16/20%, 14/25% and 16/20%, respectively.

Results: The impact of UGT1A1 genetic polymorphism on safety in unresectable pancreatic cancer patients receiving FOLFIRINOX therapy: A subset analysis of JASPAC 06 study


1Division of Gastroenterological Oncology, Shizuoka Cancer Center, Shizuoka, Japan; 2Department of Clinical Oncology, ichi Medical University Hospital, Tochigi, Japan; 3Department of Gastroenterology and Hepatology, Pancreatic Oncology, National Cancer Center Hospital, Tokyo, Japan; 4Department of Gastroenterology, Ichigaya Cancer Center Hospital, Nagoya, Japan; 5Department of Gastroenterology, Hepatobiliary and Pancreatic Medical Oncology Division, Kanagawa Cancer Center, Yokohama, Japan; 6Department of Gastroenterology, National Hospital Organization Yotsukaku Cancer Center, Matsuyama, Japan; 7Department of Medical Oncology, Yokohama City University Hospital, Yokohama, Japan; 8Department of Gastroenterology and Hepatology, Hokkaido University Hospital, Sapporo, Japan; 9Division of Gastroenterology, Chiba Cancer Center, Chiba, Japan; 10Division of Medical Oncology, Kyorin University Faculty of Medicine, Tokyo, Japan; 11Department of Chemotherapy and Internal Medicine, Toyama Prefectural Central Hospital, Toyama, Japan; 12Department of Surgery, Kinda University Faculty of Medicine, Okayama, Japan; 13Department of Medical Oncology, Tochigi Cancer Center, Tochigi, Japan; 14Department of Medical Science, Osaka Sanyo Co., Ltd, Tokyo, Japan; 15Post-Marketing Surveillance Pharmacovigilance Department, Yakult Honsha Co., Ltd, Tokyo, Japan; 16Clinical Trial Promotion Section, Shizuoka industrial Foundation Pharma Valley Center, Tokyo, Japan; 17Division of Gastroenterological Oncology, Shizuoka Cancer Center, Shizuoka, Japan; 18Clinical Trial Promotion Section, Shizuoka industrial Foundation Pharma Valley Center, Tokyo, Japan.

Table: 739P Baseline Characteristic

<table>
<thead>
<tr>
<th>Trait</th>
<th>NAX</th>
<th>NAG</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPC</td>
<td>90-100</td>
<td>34 (81%)</td>
</tr>
<tr>
<td>Age</td>
<td>70-80</td>
<td>8 (19%)</td>
</tr>
<tr>
<td>Median</td>
<td>66</td>
<td>63</td>
</tr>
<tr>
<td>Median</td>
<td>44-75</td>
<td>29-75</td>
</tr>
<tr>
<td>G1</td>
<td>9 (22%)</td>
<td>8 (19%)</td>
</tr>
<tr>
<td>CA199</td>
<td>&gt;ULN</td>
<td>32 (76%)</td>
</tr>
<tr>
<td>Median</td>
<td>1413</td>
<td>154</td>
</tr>
</tbody>
</table>
Conclusions: Treated with original FOLFIRINOX regimen, pts with UGT1A1 heterozygous type experienced severe toxicities more frequently than those with wild type. In such cases, careful management of not only hematologic but gastrointestinal toxicities seems to be needed.

Legal entity responsible for the study: Shizuoka Industrial Foundation Pharma Valley Center


471P Prognostic value of baseline neutrophil-to-lymphocyte ratio for predicting clinical outcome in metastatic pancreatic ductal adenocarcinoma (mPDAC) patients treated with liposomal irinotecan (nal-IRI) + 5-fluorouracil and leucovorin (5-FU/LV) vs 5-FU/LV alone


1Oncology, The Christie NHS Foundation Trust, Manchester, UK, 2Oncology, National Health Research Institutes, Taichung, Taiwan, 3Gastroenterology and Hepatology, Taipan Veterans General Hospital, Taipei, Taiwan, 4Oncology, Egyesület Szent István és Szent László Kórház – Rendelőház, Budapest, Hungary, 5Oncology, St. John of God Hospital, Subiaco, Australia, 6Oncology, Seoul National University Hospital, Seoul, Republic of Korea, 7GI and Lymphoma Research Unit, Royal Marsden Hospital NHS Foundation Trust, London, UK, 8Solid Tumor Translational Oncology, University Hospital Essen Westdeutsches Zentrumum, Essen, Germany, 9Oncology, Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA, 10Global Medical Affairs, Oncology, Shire, Zug, Switzerland, 11Medical Affairs, Oncology, Ipsen Biopharmaceuticals, Inc., Basking Ridge, NJ, USA, 12Oncology, Translational Genomics Research Institute, Phoenix, AZ, USA, 13Oncology, Washington University School of Medicine, St. Louis, MO, USA

Background: Elevated baseline neutrophil-to-lymphocyte ratio (NLR), a marker of subclinical inflammation, is associated with poor survival in several malignancies including mPDAC. Here we report the association of NLR with overall survival (OS) and progression-free survival (PFS) in a post-hoc analysis of the NAPOLI-1 trial (NCT01494506), that demonstrated improved survival with nal-IRI + 5-FU/LV vs 5-FU/LV for treatment of mPDAC patients (pts) after disease progression following gemcitabine-based therapy.

Methods: Pts treated with nal-IRI + 5-FU/LV or 5-FU/LV and available baseline NLR data were included (data cutoff: Nov 16, 2015). OS and PFS were assessed in pts with high (≥5) or low (<5) baseline NLR in individual and pooled treatment arms.

Results: Baseline NLR was available for 221 pts: 116/117 nal-IRI + 5-FU/LV pts and 105/105 5-FU/LV pts. In the pooled treatment arms, pts with NLR ≥5 had significantly better OS compared to pts with NLR <5 (6.2 vs 3.7 months, HR = 0.7, p = 0.02).

Interestingly, this improvement in OS in pts with low vs high NLR was significant in the nal-IRI + 5-FU/LV arm (8.4 vs 4.3 months, HR = 0.5, p = 0.001) but not in the 5-FU/LV arm (4.8 vs 3.1 months, HR = 0.9, p = 0.6). Similarly, PFS was significantly higher in pts with NLR <5 vs NLR ≥5 in the pooled treatment arms (2.7 vs 1.4 months, HR = 0.7, p = 0.05), and the nal-IRI + 5-FU/LV arm (4.2 vs 1.4 months, HR = 0.5, p = 0.002), but not the 5-FU/LV arm (1.5 vs 1.4 months, HR = 1.1, p = 0.6).

Conclusions: Data from these exploratory analyses are consistent with previous reports on the prognostic value of baseline NLR in mPDAC, and extend it to the post-gemcitabine setting. Median OS and PFS were improved in pts with low vs high baseline NLR in the nal-IRI + 5-FU/LV arm but not in the 5-FU/LV arm. Clinical implications of these data remain to be determined.

Clinical trial identification: NCT01494506

Legal entity responsible for the study: Merrimack Pharmaceuticals, Inc.

Funding: Ipsen Biopharmaceuticals, Inc.


473P Tumor hyaluronan (HA) is a novel biomarker: Results of the randomized phase 2 HALO 202 study of PEGPH20 plus nab-paclitaxel/gemcitabine (PAG) vs AG in previously untreated, metastatic pancreatic ductal adenocarcinoma (mPDAC)


1Cedars-Sinai Medical Center, Samuel Oschin Cancer Center, Los Angeles, CA, USA, 2Ninewell’s Oncology, Ostend, Belgium, Oxford, UK, 3Division of Hematology-Oncology, Beth Israel Deaconess Medical Center, Boston, MA, USA, 4Invision Center, University of California - Irvine, Irvine, CA, USA, 5Oncology, The Johns Hopkins University Hospital, Baltimore, MD, USA, 6Oncology, Scripps Cancer Center, La Jolla, CA, USA, 7Yermos/Oncal, Founders Hospital and Medical College of Wisconsin, Milwaukee, WI, USA, 8Medical Oncology, Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA, 9Medical Oncology, University of Michigan, Ann Arbor, MI, USA, 10Oncology, University of Pittsburgh Medical Center Cancer Pavilion, Pittsburgh, PA, USA, 11Oncology, University of Washington School of Medicine, Seattle, WA, USA, 12Biostats/Data Management, Ventana Medical Systems, Inc., Tucson, AZ, USA, 13Clinical, Halozyme Therapeutics, San Diego, CA, USA, 14Oncology, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Background: PEGPH20 (P) degrades HA in the tumor microenvironment to increase access to and therapeutic index of anticancer agents. In Stage 1 of this study, Halozyme Therapeutics, Inc. and Ventana Medical Systems, Inc., co-developed a novel HA assay, scoring algorithm, and cut-point, and showed improved progression-free survival (PFS) and objective response rate (ORR) in HA-High patients (pts) with PAG vs AG.

Table: 471P

<table>
<thead>
<tr>
<th>Table: 471P</th>
<th>Pooling treatment arms</th>
<th>nal-IRI + SFU/LV</th>
<th>SFU/LV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline NLR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td>&gt;5</td>
<td>&gt;5</td>
<td>&gt;5</td>
</tr>
<tr>
<td>(n = 155)</td>
<td>(n = 66)</td>
<td>(n = 154)</td>
<td>(n = 153)</td>
</tr>
<tr>
<td>6.2 (5.2 - 7.6)</td>
<td>3.7 (3.1 - 4.4)</td>
<td>8.4 (6.1 - 10.2)</td>
<td>4.3 (3.4 - 4.7)</td>
</tr>
<tr>
<td>0.7</td>
<td>0.3</td>
<td>0.5</td>
<td>0.9</td>
</tr>
<tr>
<td>5%</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR 2</td>
<td>0.7</td>
<td>0.3 - 0.8</td>
<td>0.5</td>
</tr>
<tr>
<td>2.7 (2.4 - 3.3)</td>
<td>1.4 (1.4 - 1.6)</td>
<td>2.7 (2.4 - 3.3)</td>
<td>1.4 (1.4 - 1.6)</td>
</tr>
</tbody>
</table>
Due to an imbalance in thromboendothelial (TE) events in the PAG arm, the protocol was amended to add enoxaparin and exclude pts at high risk for TE events in Stage 2, which prospectively validated the algorithm and cut-point for the VENTANA HA RxD assay.

**Methods:** In Stage 2, pts with mPDCA were randomized 2:1 to PAG (P 1 µg/kg IV 2x/wk x 3 wk [C1]), then 1x/wk x 3 wk (C2+) + AG vs AG every 28 days. Endpoints were: primary—PFS and TE events; secondary—PFS by HA level, ORR; OS by HA level was exploratory. Tumor HA was evaluated using the VENTANA HA RxD assay and algorithm; HA-High was defined by HA staining in the extracellular matrix ≥50% of the entire tumor surface at any intensity.

**Results:** 153 pts were enrolled; 123 pts were treated. As of December 16, 2016, an improvement in median PFS (91%) and median OS (50%) was observed in HA-High pts treated with PAG vs AG (Table), supporting tumor HA as a predictive marker for PEGPH20 efficacy. Among AG-treated pts, those with HA-High tumors showed poorer median PFS and median OS outcomes, suggesting that targeting tumor HA with PEGPH20 may improve the standard of care in mPDCA.

<table>
<thead>
<tr>
<th>HA-High</th>
<th>PAG</th>
<th>AG</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS, months</td>
<td>8.6</td>
<td>4.5</td>
<td>0.63 (0.21-1.93)</td>
</tr>
<tr>
<td>OS, months</td>
<td>11.7</td>
<td>7.8</td>
<td>0.52 (0.22-1.23)</td>
</tr>
<tr>
<td>HA-Low</td>
<td>n = 53</td>
<td>n = 23</td>
<td></td>
</tr>
<tr>
<td>PFS, months</td>
<td>6.0</td>
<td>7.2</td>
<td>1.21 (0.63-2.50)</td>
</tr>
<tr>
<td>OS, months</td>
<td>11.9</td>
<td>10.2</td>
<td>0.69 (0.38-1.23)</td>
</tr>
</tbody>
</table>

**Conclusions:** This is the first randomized Phase 2 study evaluating and supporting tumor HA as a potential predictive biomarker informing patient selection for PEGPH20 treatment, based on improvement in both PFS and OS in HA-High pts. The results provide support for the ongoing phase 3 HALO 109-301 study with co-primary endpoints of PFS and OS. NCT01639487.

**Clinical trial identification:** NCT01639487

**Legal entity responsible for the study:** Halozyme Therapeutics, Inc.

**Funding:** Halozyme Therapeutics, Inc.


**Background:** Median overall survival on 2nd line therapy of PDAC with 5-FU/LV plus oxaliplatin or naltirosinotec is ~5-6 m. PDAC is refractory to immune therapies and mutational burden is relatively low and tumor infiltrating CD8+ T cells are rare. AM0010 stimulates survival, expansion and cytotoxicity of intratumoral CD8+ T cells and induced immune activation, durable stable disease and a 1 yr survival of 22.5% in salvage PDAC pts. AM0010 has synergistic immune and anti-tumor activity with platinum and 5-FU in preclinical models.

**Methods:** This phase 1b clinical study studied the safety and efficacy of AM0010 + FOLFOX as 2nd line treatment of PDAC. Pts who progressed on a median of 2 prior therapies (range 1-5) were treated with AM0010/LV (5ng/kg, q2d) + FOLFOX (n = 21). The safety population (n = 25) included four additional pts with prior FOLFOX. Tumor responses were assessed using irRC. Serum cytokines, activation of blood derived T cells and peripheral T cell clonality were analyzed. Pre-existing tumor infiltrating CD8 T cells were quantified by IHC.

**Results:** AM0010 + FOLFOX was generally well tolerated. G3/4 TAEs included thrombocytopenia (52%), anemia (40%) and neutropenia (36%). Most cytopenias were transient and met remission criteria within 2-5 days. A modified AM0010 dose schedule of 5 days on, 2 days off avoided G3/4 cytopenias while retaining the immune stimulation. As of 05/1/2017, 2 pts have remained on treatment for >72 weeks. 19 pts had tumor assessment following irRC (2 CR, 1 PR, 11 SD). The ORR and DCR were 15.8% and 74%. With a median follow-up of 14.2 m (range 6.8-18.9), 10 patients were alive (48%), mPFS and mOS were 3.5 and 10.2 m. Treatment induced a sustained cytokine increase in the serum and an expansion of novel T cell clones in the blood. This and a higher number of intra-tumoral CD8 T cells correlated with increased OS.

**Conclusions:** The combination of AM0010 with FOLFOX is well tolerated in patients with metastatic PDAC. This regimen induced sustained immune activation including the expansion of oligoclonal T cells. The prolonged tumor responses and OS are encouraging in this advanced population. This regimen is being studied in a phase 3 trial.

**Clinical trial identification:** NCT02009449

**Legal entity responsible for the study:** Armo Biosciences

**Funding:** ARMO Biosciences

**Disclosure:** A. Hung, G. Brown: Employee of ARMO Biosciences. P. Van Vlaselet: Stock, leadership, employee of ARMO Biosciences. M. Orte: Employee of ARMO: Stock. All other authors have declared no conflicts of interest.

**Background:** Circulating levels of ADAM12, a stromal activation biomarker, are predictive of survival in pancreatic ductal adenocarcinoma (PDAC)

**Methods:** The prognostic and predictive value of ADAM12 was determined in an institutional cohort from the Academic Medical Center (AMC), which included 144 pts with PDAC (58 resected and 86 non-resected pts) and 38 non-age–matched healthy controls, and in a cohort of 372 pts with metastatic PDAC treated with sub-paclitaxel plus gemcitabine (sub-PGem) or Gem alone in the MACACT trial.

<table>
<thead>
<tr>
<th>HA-High</th>
<th>PAG</th>
<th>AG</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS, months</td>
<td>8.6</td>
<td>4.5</td>
<td>0.63 (0.21-1.93)</td>
</tr>
<tr>
<td>OS, months</td>
<td>11.7</td>
<td>7.8</td>
<td>0.52 (0.22-1.23)</td>
</tr>
<tr>
<td>HA-Low</td>
<td>n = 53</td>
<td>n = 23</td>
<td></td>
</tr>
<tr>
<td>PFS, months</td>
<td>6.0</td>
<td>7.2</td>
<td>1.21 (0.63-2.50)</td>
</tr>
<tr>
<td>OS, months</td>
<td>11.9</td>
<td>10.2</td>
<td>0.69 (0.38-1.23)</td>
</tr>
</tbody>
</table>
Table 745P

<table>
<thead>
<tr>
<th>Overall Population</th>
<th>nab-P/Gem Arm</th>
<th>Gem Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Deaths, n/N (%)</strong></td>
<td><strong>Deaths, n/N (%)</strong></td>
<td><strong>Deaths, n/N (%)</strong></td>
</tr>
<tr>
<td>Median OS (95% CI), mo</td>
<td>Median OS (95% CI), mo</td>
<td>Median OS (95% CI), mo</td>
</tr>
<tr>
<td>FC &lt; 1</td>
<td>98/112 (88)</td>
<td>52/59 (88)</td>
</tr>
<tr>
<td>FC &gt; 1</td>
<td>54/58 (93)</td>
<td>25/27 (93)</td>
</tr>
<tr>
<td>ND</td>
<td>30/38 (79)</td>
<td>17/22 (77)</td>
</tr>
</tbody>
</table>

**Results:** For the AMC cohort, higher serum ADAM12 levels (median, 372 pg/mL; P < .01) were found in pts with PDAC vs healthy controls (median, 154 pg/mL). High ADAM12 levels (> median) were significantly associated with poor survival (P = .04) in resected pts but not in non-resected pts (P = .67). In the pooled MPACT analysis, median overall survival (OS) was significantly longer (9.3 vs 6.9 months; log-rank P = .01) in pts with no detectable (ND; n = 95) vs detectable (n = 277) serum ADAM12 levels at baseline (BL). Median OS was longer in pts with ADAM12 decrease (fold change [FC] < 1) vs increase (FC > 1) from BL to cycle 2, but both OS values were significantly shorter than that in pts with ND ADAM12 levels at either time point (Table).

In a multivariate analysis, baseline ADAM12 levels (0 vs > 6; P = .02), treatment (nab-P/Gem vs Gem; P = .02), and Karnofsky performance status (90-100 vs 70-80; P < .01) were significant predictors of OS. OS in pts with PDAC measured at both BL and cycle 2 in the MPACT study.

Conclusions: Low serum levels of ADAM12 at baseline were associated with longer OS in pts with PDAC, as were decreases in ADAM12 during treatment. ADAM12 may be a valuable biomarker to predict long-term outcomes in pts treated with nab-P/Gem.

Legal entity responsible for the study: Celgene Corporation

Funding: Celgene Corporation

Disclosure: H.W. van Laarhoven: Advisory role, Lilly, Nordic. Research funding to institution: Bayer, BMS, Celgene, Lilly, MDS, Nordic, Roche. J.P. Modena: Employment (family member) Sanofi, Abbott/Abbvie; stock ownership (family member), Sanofi; advisory role, Biovionex, patents, royalties, other IP, Aduro Biotech. J. Shian songLiu, R. Jiang, D.W. Pierce: Employment, stock ownership, Celgene. M.F. Bijnens: Research funding, Celgene; travel & accommodations, Biouniversa. All other authors have declared no conflicts of interest.

Table 746P

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Prognostic characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Age</td>
</tr>
<tr>
<td>Albumin</td>
<td>Albumin</td>
</tr>
<tr>
<td>Biliary stent</td>
<td>Bilirubin</td>
</tr>
<tr>
<td>CA19.9</td>
<td>CA 19.9</td>
</tr>
<tr>
<td>C-Reactive Protein (CRP)</td>
<td>CRP</td>
</tr>
<tr>
<td>Disease status</td>
<td>Disease status</td>
</tr>
<tr>
<td>Gender</td>
<td>Gender</td>
</tr>
<tr>
<td>Histology</td>
<td>Histology</td>
</tr>
<tr>
<td>LDH</td>
<td>LDH</td>
</tr>
<tr>
<td>Liver metastasis</td>
<td>Liver metastasis</td>
</tr>
<tr>
<td>Loss of weight &gt; 10%</td>
<td>Number of metastatic sites</td>
</tr>
<tr>
<td>Neutrophil lymphocyte ratio (NLR)</td>
<td>Pain at baseline</td>
</tr>
<tr>
<td>Number of metastatic sites</td>
<td>Performance status</td>
</tr>
<tr>
<td>Pain at baseline</td>
<td></td>
</tr>
<tr>
<td>Performance status</td>
<td></td>
</tr>
<tr>
<td>Peritoneal metastasis</td>
<td></td>
</tr>
<tr>
<td>Primary tumor location</td>
<td></td>
</tr>
<tr>
<td>Prior chemotherapy/radiotherapy</td>
<td></td>
</tr>
<tr>
<td>Prior surgery</td>
<td></td>
</tr>
<tr>
<td>Pulmonary metastasis</td>
<td></td>
</tr>
<tr>
<td>Time from diagnosis</td>
<td></td>
</tr>
<tr>
<td>Tumor differentiation</td>
<td></td>
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<tr>
<td>Weight/BMI</td>
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</tbody>
</table>

**Conclusions:** The COmmuniCation statement on Mandatory Measurements identifies a set of baseline- and prognostic characteristics in unresectable Pancreatic Cancer Trials (COMM-PACT) that allows for adequate comparison of outcomes between studies.

Legal entity responsible for the study: Not applicable

Funding: None

Disclosure: All authors have declared no conflicts of interest.


Results: A total of 624 studies were identified. After screening, 39 randomized controlled trials (RCTs) with 15,863 patients were included. Thirty-two baseline characteristics and 26 prognostic characteristics were identified. After two consensus rounds, 24 baseline characteristics and twelve prognostic characteristics were designated as a mandatory reporting set for future trials. Table 1. Mandatory set reporting frequencies of baseline characteristics and prognostic relevance of identified variables. A modified Delphi panel of two rounds involving 23 leading medical-oncologists in the field of pancreatic cancer was used to develop the consensus.
Background: Resminostat is an oral hydroxamate-type inhibitor of class I, IIb, and IV histone deacetylases. S-1 is preferably used in biliary tract (BTC) and pancreatic cancer (PC) in Japan. However, patients (pts) with high thymidylate synthase (TS) expression are selected for S-1 combination therapy in a 2nd-line or later setting for BTC/PC. Here we describe MSEs observed in a phase 2 study of PEGPH20 (P) with the regimen selected in the first stage. Dose-limiting toxicities (DLTs) were evaluated according to adverse drug reactions observed during the first cycle in the first stage.

Results: A total of 27 pts were enrolled (first stage: R1, 6 pts; R2, 5 pts; R3, 6 pts; second stage: 10 pts). Two DLTs were observed: one (Grade 1 anorexia) in a patient treated with R2 and one (Grade 5 stomatitis) in another patient treated with R3. Dose modification due to gastrointestinal toxicities was implemented frequently in pts treated in the first stage. Therefore, R3 was selected as the regimen for the second stage. A total of 16 pts (BTCR: 3 pts; PC: 3 pts) were treated with R3 and it was well-tolerable. Disease control rate was 81.3% (BTC: 84.6%; PC: 86.7%). The median progression-free survival was 3 months (BTC: 5.5 months; PC: 2.3 months).

Conclusions: The data revealed that R3 (5 + 2" dosing schedule of resminostat in combination with S-1) was well tolerated in advanced BTC/PC pts. Further investigations are warranted for its efficacy especially in advanced BTC/PC pts.

Clinical trial identification: NCT01528641

Legal entity responsible for the study: Yakult Honsha Co., Ltd.

Funding: Yakult Honsha Co., Ltd.


474P

Comparisons of outcomes of patients with advanced pancreatic cancer (APC) treated with FOLFIRINOX (FX) versus gemcitabine and nab-paclitaxel (GN): A population-based cohort study


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Background: FX and GN are more active than gemcitabine in patients with APC. However, it is not known if FX is superior to GN in APC. In the absence of a randomized controlled trial this population-based cohort study is undertaken to compare efficacy and safety of the two standard regimes in APC.

Methods: All patients with newly diagnosed locally APC in the province of Saskatchewan, Canada, during 2011-2016 who received FX or GN, were assessed. A Cox proportional multivariate analysis was done to evaluate correlation of chemotherapy regimen and survival.

Results: 119 eligible patients with median age of 61 yrs (IQR: 56-67) & M:F of 70:49 were identified. 93% had WHO performance status (PS) of 0 or 1, and 77% had metastatic PC. 15% received adjuvant therapy and 33% had 2 metastatic sites. Of 119 patients, 86 (72%) received FX and 33 (28%) treated with GN. There were significant differences between the two groups with respect to age (58 vs. 64 yrs), WHO PS of 2 (28% vs. 15%) and metastatic disease (81% vs. 64%), in FX and GN groups, respectively. Median progression-free survival of FX group was 6 months (95% CI: 4.5-7.5) vs. 4 months (2.9-5.1) with GN (p = 0.39). Median overall survival (OS) with FX was 9 months (7.1-11) vs. 9 months (4.2-13.8) with GN (p = 0.081). At 12 months 26% & 27% patients were alive in FX and GN groups, respectively. Median OS of patients who received 2nd line therapy was 15 months (10.5-19.5) vs. 8 months (6.3-9.7) with no v+ line therapy (0.009). Patients in FX had higher incidences of any grade diarrhea (52% vs. 18%), mucositis (21 vs. 3), neuropathy (65 vs.36) and thromboembolism (34 vs. 9%) whereas GN group had renal toxicity 18% (5 vs. 18%) and neutropenia 26% (12 vs. 8%) in FX and GN groups respectively. OS differences between the two groups with respect to age (58 vs. 64 yrs), WHO PS of 2 (28% vs. 15%) and metastatic disease (81% vs. 64%), in FX and GN groups, respectively.

Conclusions: Our results showed that real world patients with APC treated with FX or GN had comparable survival with different safety profiles. In this selected patients who received combination therapy, male gender and subsequent treatment were correlated with better survival.

Legal entity responsible for the study: N/A

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Musculoskeletal Events (MSEs) with PEGPH20 treatment and management in patients with previously untreated metastatic pancreatic ductal adenocarcinoma (mPDAC)

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Background: Hyaluronan (HA) accumulation in the tumor microenvironment is associated with poor outcomes. Pegylated recombinant human hyaluronidase PH20 (PEGPH20) degrades HA, facilitating access of cancer therapies. MSEs (e.g., muscle spasms, arthralgia, and myalgia) occur frequently with PEGPH20, and were dose-limited in Phase 1 studies. Here we describe MSEs observed in a phase 2 study of PEGPH20 (P) plus gemcitabine/nab-paclitaxel (AG) as AG in patients with previously untreated mPDAC.

Methods: In Stage 1 of the study, patients were randomized 1:1 to PAG or AG (P 33 mg/kg IV weekly x 2 weeks in Cycle 1, then once weekly x 3 weeks in Cycle 2) every 28 days. A clinical hold due to an imbalance in thromboembolic events resulted in ~40% of patients discontinuing PEGPH20. After the clinical hold, patients were randomized 2:1 to PAG or AG (Stage 2). Dexa-methasone 8 mg was administered orally within 2 hours before and 8-12 hours after PEGPH20 to lessen the severity of MSEs. We analyzed adverse event frequency, severity, timing, and management.

Results: 279 patients were enrolled, 260 patients comprised the safety population. All patients received a median of 3.8 months of study treatment. The proportion of patients with treatment-emergent MSEs was higher in the PAG arm vs AG arm (45% vs 43% in the first cycle, 33% vs 29% in Cycle 2, and 31% vs 30% in Cycle 3). Median time to MSE onset was 2 (0-287) days for PAG and 8 (0-46) days for AG. Median duration of Grade 3 MSEs was 9 (5-14) days for PAG vs 8.5 (2-22) days for AG. Five (4%) patients experienced MSEs that led to PAG discontinuation: muscle spasms (n = 4) and myalgia (n = 1). Medications were administered in 57% (PAG) vs 20% (AG) of MSE episodes, predominantly to manage Grade 3 MSEs.

Conclusions: MSEs are commonly observed with AG treatment, and even more frequently with PAG. MSEs are primarily mild (Grade 1/2) and infrequently lead to treatment discontinuation. The time course, associated dose modifications, and management of MSEs will be presented.

Clinical trial identification: NCT01893487

Legal entity responsible for the study: Halozyme Therapeutics, Inc.

Funding: Halozyme Therapeutics, Inc.

Background: CCL2/CCR2 plays a key role in immunosuppressive properties of the pancreatic adenocarcinoma tumor microenvironment (TME), patients’ prognosis and chemoresistance. PF-04136309 (oral CCR2 inhibitor) blocks recruitment and migration of inflammatory monocytes (IM) from bone marrow (BM) to TME.

Methods: This ongoing multicentre phase Ib study is investigating PF-04136309 in combination with nab-paclitaxel and gemcitabine (nab-P+Gem) in pts previously untreated metastatic ductal adenocarcinoma of the pancreas (mPDAC). Objectives: primary; safety, tolerability, maximum tolerated dose, recommended dose; secondary: pharmacokinetics (PK), pharmacodynamics of PF-04136309; exploratory: efficacy, proof of mechanism (POM), as CCR2 inhibition trapped IMs in BM and decreased IMs in peripheral blood and metastatic tumor tissue with paired tumor biopsies and bone marrow aspirates at baseline and at 1 or 2 cycles.

Results: From May 1, 2016—March 17, 2017, 21 pts (ECOG PS 0-1; mean age 61.8 yrs; range 46-79) received PF-04136309. Cohort 1, starting dose level: 1 grade 3 drug-related DLT (apoptosis disorder), grade 2 and 2 grade 1 rashes. Cohort 2 (1 dose level reduction): 4 (23.5%) grade 3 drug-related DLT (1 scalp dysesthesia, 1 ALT-AST, 1 pneumonia, 1 pts). Recommended total daily dose 1000mg. With median duration of treatment of 4 mos (1-9), grade 2 drug-related AEs: neutropenia 3 (17.6%), fatigue 4 (23.5%), diarrhea 1 (5.9%), lung toxicities 3 (17.6%); 1 pts with dose reduction: nab-P 47%, Gem 53%, PF-04136309 41%; median relative dose intensity: nab-P 84%, Gem 67%, PF-04136309 80%. Early objective response in 10 evaluable pts: PR 6 (60%), SD 1 (10%), PD 3 (30%). Disease control rate at 4 mo 79%. Median PFS not reached (8 pts on treatment). PF-04136309 PPK was consistent with previous single agent studies. Almost all had a drop in peripheral blood CD14+CCR2+ monocytes (baseline-Day 15). IMs decreased and CD4+ and CD14−/CD16+ T cells increased (5-8 fold) in paired biopsy samples. One of 2 pts had increased tumor associated CD1+CD4+ and PD-1+CD8+ T cells.

Conclusions: Encouraging safety, favorable PK, clinical responses and POM with CCR2 inhibition plus nab-P+Gem in mPDAC pts.

Clinical trial identification: NCT02732398.

Legal entity responsible for the study: Pfizer Inc.

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Disclosure: M. Noel: Speaker’s bureau for Taiho Oncology. M. Lowery: Advisory paid to institution. Pfizer. B. Jin, C.T. Taylor, B.J. Ganguly, D. Yin, L.E. Cemelin, D.A. Wunderlich: Employee and stockholder of Pfizer Inc. All other authors have declared no conflicts of interest.

751P Metastatic pancreatic cancer: Real Life data from the german quality of life and translational research on pancreatic cancer study (Qolixane)


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Background: The data of FOLFIRINOX as second-line chemotherapy in advanced pancreatic cancer is very limited. The JASPAC06 study, a nationwide multicenter observational study of FOLFIRINOX for the patients with unresectable or recurrent pancreatic cancer as any line treatment, showed the favorable efficacy and safety in Japanese clinical practice.

Methods: The subjects were the patients with unresectable/recurrent pancreatic cancer who received FOLFIRINOX as second-line chemotherapy.

Results: Of the 399 evaluable patients in the JASPAC06 study, 44 patients were eligible. Patients characteristics were: median age, 62 years; male, 26 (59%); ECOG PS0-1, 30 (68%) 1/2 13%); disease status recurrent/metastatic, 4 (9%) 8(18%) 9 (23%); biliary drainage, 11 (25%); UGT1A1 status *28*6 wild/singl heterozy/ous/homzyous or double heterozy/ous/unknown, 25 (57%) 16/36/215/122%. The initial dose was reduced in 28 (64%) patients. The median time to treatment failure and the number of cycles were 4.5 (range, 6-373) days and 6 cycles (range, 1-13 or more). The major grade 3/4 adverse events were neutropenia in 29 (66%) patients, leucopenia in 17 (39%), anorexia in 17 (33%), febrile neutropenia in 5 (17%) and anemia in 5 (17%). Fatal adverse event occurred in 1 patient, which was a sudden death. The median overall survival, progression free survival and 1-year survival rates were 18.1 (95%CI, 7.3-1.13), 4.1 (95%CI, 1.5-8.4) months and 41.0%, respectively. The overall response rate and disease control rate were 28% and 65%. The reason for discontinuation of FOLFIRINOX, excluding 2 patients ongoing treatment, were tumor progression in 38(66%) and toxicity in 4(9%).

Conclusions: It was suggested that FOLFIRINOX as second-line chemotherapy in advanced pancreatic cancer was effective for the patients with good PS and toxicity was similar to that as the first-line treatment.

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Legal entity responsible for the study: N/A

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753P Quality of life (QoL) of patients (pts) with metastatic pancreatic cancer (mPAC) initiating first-line chemotherapy (CT) in routine practice

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Background: Considering the physical decline of mPAC pts, the assessment of QoL becomes a matter of major concern. We aimed to assess the QoL of mPAC pts treated with first-line CT in routine practice.

Methods: Observational, prospective, multicenter study including mPAC pts who started first-line CT between 2014 and 2015 in 12 Spanish centers. Treatment and clinical characteristics were recorded at CT start (baseline [BL]). The pts’ QoL, ECOG, and Karnofsky index (KI) were measured at BL, at days 15 and 30, and every 4 weeks up to 6 mo of CT. QoL was measured using the EORTC QLQ-C30 global health status questionnaire (QLQ). Other variables included treatment response, overall survival (OS), and progression-free survival (PFS).

Results: The study sample included 117 pts with a median age of 65 years (range 37-84). Metastases were mostly hepatic (75%). At BL, median weight loss (last 3 mo) was 9.2%, ECOG was 0-1 in 22% and 82% of pts, respectively, and KI was 70-80 in 48% and 52% of pts, respectively. Main first-line CT was gemcitabine in monotherapy (19%) or combined with nab-paclitaxel (65%). Overall, median OS and PFS were 9.0 mo (95% CI 6.4-10.6) and 6.0 mo (4.6-7.8), respectively; 3% and 28% of pts achieved a complete and partial response, respectively, with stable disease in 39% of pts. During the follow-up, 64% of pts improved their QoL, the KI showed no significant changes. Of 19 pts with BL ECOG 2, between 67% and 100% had improved their QLQ score at visits at the 1st mo and following. At BL, pts with KI 70-80 had poorer QoL, but experienced a greater improvement than those with KI 90-100 (p = 0.013), reaching similar QLQ scores after 2 mo of CT. A similar trend was observed in pts with ECOG 0-1 vs 2 (p < 0.001). Pts improved their QoL irrespective of their weight loss, but those with weight loss <10% had greater QLQ scores throughout the follow-up (p = 0.028). Median OS was higher in pts with BL QLQ ≤50 (p = 0.015), KI 90-100, and weight loss ≤10% were associated with a greater OS. Most pts improved their QoL during CT, including those with poorer ECOG and KI at BL.

Clinical trial identification: CEL-CPM-2014-01

Legal entity responsible for the study: Celgene, S.L.

Funding: Celgene, S.L.

Disclosure: M. Martin, A. Garcia: Temporary consultant collaborator with Celgene. L. Pellen, D. Vilanova: Employee of Celgene. All other authors have declared no conflicts of interest.

754P Impact of the duration of diabetes mellitus (DM) on the outcomes of metastatic pancreatic cancer (mPAC) treated with gemcitabine (G): A retrospective study

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Background: While previous studies showed that patients (pts) with PC and long-standing DM had worse survival than pts without DM, the impact of the duration of DM on therapeutic outcomes has not been sufficiently studied in pts receiving chemotherapy for mPC.

Methods: We retrospectively analyzed the therapeutic results for pts with mPC who received G as standard therapy before the introduction of combination regimens at two sites of the National Cancer Center (“Tokyo” and “Kashiwa”). The efficacies and toxicities of G were compared among three groups classified by the DM duration: no DM, short-term DM (<4 years), and long-term DM (>4 years). To examine the associations of the DM duration with overall survival (OS) and progression-free survival (PFS), Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) adjusted for the baseline characteristics.

Results: Overall, 350 pts (“Tokyo” n = 202, 2008-2013; “Kashiwa” n = 148, 2008-2011) were included. 218, 87, and 45 in the no DM, short-term DM, and long-term DM groups, respectively. No statistically significant differences in baseline characteristics were observed among the three groups except for BMI (median [kg/m2]: 20.7, 21.4, and 22.5; p = 0.015, Kruskal-Wallis test). Compared with the no DM group, multivariable-adjusted HRs for PFS were 1.33 (95% CI, 0.94-1.89; p = 0.103) for the long-term DM group and 1.12 (95% CI, 0.85-1.47; p = 0.410) for the short-term DM group; and those for OS were 1.57 (95% CI, 0.95-1.98; p = 0.096) and 1.10 (95% CI, 0.82-1.46; p = 0.533), respectively. There were no substantial differences in HRs between “Tokyo” and “Kashiwa” (e.g., HRs of long-term DM for PFS were 1.34 [95% CI, 0.96-2.44] and 1.33 [95% CI, 0.80-2.21], respectively; HRs of long-term DM for OS were 1.32 [95% CI, 0.82-2.14] and 1.34 [95% CI, 0.60-2.26], respectively). Also, HRs for PFS and OS did not substantially change with different cutoff years of DM duration (ranges of HRs of long-term DM with cutoff at 3-5 years: PFS, 1.36-1.55; OS, 1.21-1.33). No significant differences in tumor response and toxicity were observed.

Conclusions: A long pretreatment history of DM may be associated with a shorter PFS and OS among pts with mPC.

Legal entity responsible for the study: National Cancer Center Hospital

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755P Prognostic value of neutrophil-lymphocyte ratio in first line treatment for metastatic pancreatic adenocarcinoma

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Background: Tumor location and pro-inflammatory microenvironment are both implicated in cancer progression and thus measures of these are thought to have important prognostic value. In this study, these readily available factors were examined in patients diagnosed with metastatic pancreatic adenocarcinoma (mPAC) being treated in first line with FOLFIRINOX (FFX) or Gemcitabine with nab-Paclitaxel (GnP).

Methods: A cohort of 79 patients diagnosed with mPAC between 2010 – 2016 and treated either with FFX or GnP first line were analyzed. The NLR was calculated based on the complete blood count obtained on the day of the first treatment. Cox proportional hazard models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) associating progression-free survival to the patients’ demographics, treatment, clinical and pathological factors. NLR was treated as a continuous covariate.

Results: Of the total patients (60% male, median age 69), 44 (58.7%) were treated with FFX. At the time of diagnosis, 20 (26.6%) presented with ECOG 0-1 vs 2 (p < 0.001). Pts improved their QoL irrespective of their weight loss, but those with weight loss <10% had greater QLQ scores throughout the follow-up (p = 0.028). Median OS was higher in pts with BL QLQ ≤50 (p = 0.015), KI 90-100, and weight loss ≤10% were associated with a greater OS. Most pts improved their QoL during CT, including those with poorer ECOG and KI at BL.

Clinical trial identification: CEL-CPM-2014-01

Legal entity responsible for the study: Celgene, S.L.

Funding: Celgene, S.L.

Disclosure: All other authors have declared no conflicts of interest.
Background: Combined treatment of nab-P plus GEM increases survival in patients with MPC. However, treatment efficacy and safety need to be assessed in real-life practice, including pts irrespective of their clinical characteristics and number of dose administered and treatment duration.

Methods: Retrospective, multicenter study including pts with MPC who started first-line treatment with nab-P plus GEM between December 2013 and June 2015 according to routine clinical practice. Overall survival (OS) and progression-free survival (PFS) were assessed for the total sample and the exploratory subgroups based on treatment and clinical characteristics of pts.

Results: 210 pts (60% males) were enrolled with a median age of 65 years (range 37 – 81); 25% were ≥ 70 years. MPC was de novo and recurrent in 78% and 22% of pts, respectively. 18% had a biliary stent. At baseline, 53% of pts had Neutrophil lymphocyte ratio (NLR) > 2.1, 32% had CA 19.9 > 35 U/mL, and 25% had ECOG > 1. Pts received a median of 4 cycles (1 – 21); 32% started treatment with a dose reduction and 17% received ≥ 30 cycles of treatment, mainly due to toxicity (33%) or progression (30%); 25% of pts achieved objective response, and median OS and PFS were 7.0 (95% CI 5.8 – 8.0) and 5.0 (4.3 – 5.9) months (mo), respectively. Compared with pts treated during 30 days, those with ≤ 30 treatment had lower OS (6.6 [7.6 – 10.2] vs. 1.9 [8.6 – 2.3] mo); p < 0.001).

Results: We report the results of a phase II study of gemcitabine, erlotinib, and S-1 in patients with advanced pancreatic cancer.

Disclosure: All authors have declared no conflicts of interest.

Background: Gemcitabine-based chemotherapy is considered as a standard front-line chemotherapy for patients with advanced pancreatic cancer. Although addition of erlotinib or S-1 to gemcitabine has resulted in the highest objective response rate (ORR), it was not associated with any survival benefit. Hence, prospective head-to-head randomized clinical trials are needed to confirm the clinical benefit of this approach.

Methods: A retrospective analysis of patients treated with gemcitabine, erlotinib, and S-1 was performed. The study included patients treated between March 2016 and October 2017, according to the following inclusion criteria: metastatic pancreatic adenocarcinoma, Unidirectional chemotherapy regimen. All patients were treated with gemcitabine and S-1 at their standard doses. Erlo tinib was commenced at 150 mg daily on days 1-21 of cycles, and dose escalation of S-1 to 45 mg/m² was permitted from second cycle for pre-defined tolerable patients.

Results: Thirty-seven patients (median age 61.5 years) were enrolled. A total of 140 cycles of chemotherapy were administered (median of 3.8, range 1-8 cycles). Toxicities were evaluated in 36 patients, and the responses were evaluated in 32 patients. Major grade 3/4 toxicities included neutropenia (25%), febrile neutropenia (2.8%), fatigue (22.2%), infection (8.8%), vomiting (5.6%), and mucositis (5.6%). The overall response rate was 12.5% (95% confidence interval (CI): 5.1-21.9) and disease control rate was 62.8% (95% CI: 48.8—76.3). The median progression-free survival and overall survival were 3.7 months (95% CI: 2.8-4.6 months) and 6.7 months (95% CI: 3.4-9.8 months), respectively.

Conclusions: The combination of gemcitabine, erlotinib, and S-1 provided an acceptable toxicity profile and modest clinical benefits in patients with advanced pancreatic cancer.
multimodal therapy including chemoradiation for the development of FN.

Multivariate logistic regression analysis showed that the pretreatment white blood cell count (WBC) < 4000/mcL (OR: 1.10, 95% CI: 1.00 to 1.20, p = 0.046), serum total bilirubin (T-Bil) > 1.0mg/dL (OR: 5.83, 95% CI: 2.28 to 14.9, p < 0.0002), tumor location in pancreatic head (OR: 2.53, 95% CI: 1.17 to 5.76, p = 0.022) and no initial dose reduction (OR: 6.13, 95% CI: 2.81 to 14.4, p < 0.0001) were significantly associated with higher risk of FN.

Conclusions: Pretreatment WBC < 4000/mcL, T-Bil > 1.0mg/dL, tumor location and no initial dose reduction might be risk factors for FN in unresectable/recurrent PC pts receiving FPF. The predictive factors proposed in our study could be utilized to select the pts at a high risk for the development of FN who may benefit from dose reduction or G-CSF prophylaxis.

Clinical trial identification: UMIN00014658

Legal entity responsible for the study: JASPAC

Funding: Yakuhon Co., Ltd., and Daiichi Sankyo Co., Ltd.


### 760P

**Risk factors for febrile neutropenia (FN) in unresectable/recurrent pancreatic cancer (PC) patients/pts receiving FOLFOXIRINOX (FFX) from JASPAC06 study**

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**Background:** FXX is considered one of the standard chemotherapy regimens for chemo-naive unresectable/recurrent PC pts with good performance status (PS), but can be associated with significant toxicity. A high incidence of FN (23%) was reported from a Japanese phase II trial of FXX. The aim of this study was to clarify the risk factors for FN in these pts.

**Methods:** We used data obtained from the JASPAC06 study. The subjects were pts with unresectable/recurrent PC who received FXX during one year from Dec. 20, 2011. All the subjects were registered and their clinical data were sent to the data center. The logistic regression model was used to estimate odds ratios (ORs) of the potential risk factors for the development of FN.

**Results:** A total of 399 pts were included in this analysis. Pts characteristics were: median age 63 years, ECOG-PS 0/1/2, 70/29/1%, disease status locally advanced/meta-static/recurrent, 20/60/20%, prior chemotherapy yes/no, 37/63/9%, biliary stent before FXX 21%, UGT1A1 polymorphism *28 and *16 wild/single heterozygous/homozygous or double heterozygous, 35/38/4%. Dose reduction at initial treatment yes/no, 68/32%. The median number of treatment cycles was 6. FN occurred in 13% of the pts. A multivariate logistic regression analysis showed that the pretreatment white blood cell count (WBC) < 4000/mcL (OR: 1.10, 95% CI: 1.00 to 1.20, p = 0.046), serum total bilirubin (T-Bil) > 1.0mg/dL (OR: 5.83, 95% CI: 2.28 to 14.9, p < 0.0002), tumor location in pancreatic head (OR: 2.53, 95% CI: 1.17 to 5.76, p = 0.022) and no initial dose reduction (OR: 6.13, 95% CI: 2.81 to 14.4, p < 0.0001) were significantly associated with higher risk of FN.

**Conclusions:** Pretreatment WBC < 4000/mcL, T-Bil > 1.0mg/dL, tumor location and no initial dose reduction might be risk factors for the development of FN in unresectable/recurrent PC pts receiving FXX. The predictive factors proposed in our study could be utilized to select the pts at a high risk for the development of FN who may benefit from dose reduction or G-CSF prophylaxis.
Impact of advances in systemic chemotherapy for unresectable pancreatic ductal adenocarcinoma (PDAC) in Alberta, Canada

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Background: Since 2011, new systemic therapy combinations, FOLFIRINOX and nab-paclitaxel with gemcitabine, have demonstrated improvements in survival for PDAC. It is unclear if the availability of these therapies has changed referral patterns or the uptake of systemic treatment in the HA-High pts. These data support HA as a potential predictive biomarker for pt selection of chemotherapy.

Methods: We performed a population-based analysis of patients with a biopsy-proven unresectable/metastatic PDAC from 2009-2016 in Alberta, Canada. The primary outcome was overall survival (OS) of patients who received chemotherapy, pre and post 2011, while controlling for relevant patient and disease characteristics. Secondary outcomes include the proportion of patients referred to a cancer centre, and receipt of systemic treatment in a universal health care system.

Results: A total of 1764 patients with PDAC were identified, with a median age of 70, 51% male, 86% metastatic disease and 59% occurring in the head or neck. 485 patients were diagnosed prior to 2011 while 1279 were diagnosed after. Rates of cancer centre referrals after 2011 increased from 44 to 59% (p < 0.03), but there was no difference in the use of initial chemotherapy (26 vs 28%, p = 0.44). Use of single agent regimens decreased (81% to 53%) in favour of combination therapy (p < 0.01). Specifically FOLFIRINOX changed from 12% to 21% and nab-paclitaxel (3 to 21%). The median OS of patients pre-2011 who received chemotherapy compared to best supportive care (BSC) was 8.4 vs 1.8 months, and post-2011 7.5 vs 1.6 months, p < 0.01. After controlling for age, sex, primary location, stage, chemotherapy use and era, there was no difference in outcomes post and pre 2011, HR 1.07, 95% CI 0.95-1.18, p = 0.31, but chemotherapy improved survival compared to BSC, HR 0.32, 95% CI 0.28-0.36, p < 0.01.

Conclusions: The natural history of PDAC remains very poor, despite advances in systemic therapy. The majority of patients are not receiving systemic chemotherapy, highlighting the need for improvements in diagnosis and referral, even in a universal health care system. There are no modern trials comparing best supportive care to modern chemotherapy, and this population-based study demonstrates a real-world benchmark for improving patient outcomes.

Legal entity responsible for the study: Tom Baker Cancer Centre

Funding: None

Disclosure: R. Lee-Yong: Advisory board: Celgene. W.Y. Cheung: Advisory Celgene: Shire. P. Tang: Advisory Board: Celgene, Shire. All other authors have declared no conflicts of interest.

Randomized phase 2 study of PEGPH20 Plus nab-paclitaxel/gemcitabine (PAG) vs AG in patients (Pts) with untreated, metastatic pancreatic ductal adenocarcinoma (mPDAC)

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Background: Hyaluronan (HA) accumulation in the tumour microenvironment produces elevated tumor pressure, vascular compression, and reduced drug delivery. PEGPH20 degrades HA, increasing the access and therapeutic index of anticancer agents.

Methods: In Stage 1 of this phase 2 study, pts with untreated mPDAC were randomized 1:1 to PAG (P = 3 mg/kg IV 2x/wk 3 wks in Cl, then 1x/wk 3 wks in C2 + plus AG) vs AG every 28 days. An imbalance in thrombosis/TE (TO) events in the PAG arm led to a clinical hold (~40% of pts discontinued PEGPH20), exclusion of pts at high risk for TE events and enoxaparin prophylaxis for all. In Stage 2, randomization was 2:1 to PAG vs AG. Tumor HA was tested using a novel assay (VENTANA HA RxDx). Primary endpoints were PFS (evaluable pts) and TE event rate (Stage 2). Secondary endpoints were PFS by HA level and ORR.

Results: 279 pts were randomized; 231 are efficacy evaluable. Of 246 pts with HA data, 84% (38/46) were HA-High. As of December 16, 2016, the primary PFS endpoint was statistically significant for PAG vs AG (HR 0.73, 95% CI 0.53-1.00; p = 0.048) (Table). PFS in HA-High pts was also statistically significant for PAG vs AG (HR 0.51, 95% CI 0.26-1.00; p = 0.048). ORR in HA-High pts was 46% (PAG) vs 34% (AG). Overall survival in HA-High pts (exploratory) was 11.5 months (mos) (PAG) and 8.5 mos (AG) (HR 0.96, 95% CI 0.57-1.61). TE events were similar (PAG 14% vs AG 10%) with enoxaparin initiation.

Table: 763P

<table>
<thead>
<tr>
<th>Population</th>
<th>Events/Total, n Median PFS, months</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AG</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy Evaluable</td>
<td>100/139, 6.0 65/92; 5.3</td>
<td>0.73 (0.53, 1.00)</td>
<td>0.048</td>
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<tr>
<td>HA-High (n = 84)</td>
<td>24/49, 9.2 19/35, 5.2</td>
<td>0.51 (0.26-1.00)</td>
<td>0.048</td>
</tr>
</tbody>
</table>

All grade treatment-related AE included peripheral edema (PAG 63% vs AG 26%), muscle spasm (56% vs 3%), neutropenia (34% vs 19%), and myalgia (26% vs 7%).

Conclusions: Randomized Phase 2 study met both primary endpoints (PFS and TE event rate), with the largest improvement in the secondary endpoint of PFS in HA-High pts. These data support HA as a potential predictive biomarker for pt selection of chemotherapy, and this population-based study demonstrates a real-world benchmark for improving patient outcomes.

Legal entity responsible for the study: Halozyme Therapeutics, Inc.

Funding: Halozyme Therapeutics, Inc.

Our results demonstrated that N-WASP is a regulator of EMT in pancreatic cancer. By identifying of N-WASP expression promoted by Snail, N-WASP and LOXL2 silenced pancreatic cancer cell which exhibited significant changes of fac- tors related to invasiveness and N-WASP expression. These findings suggest that N-WASP can be a target for the deter- mining of distant metastasis of pancreatic cancer.

Limitations

Conclusions: Our results demonstrated that N-WASP is a regulator of EMT in pancre- atic cancer. By identifying of N-WASP expression promoted by Snail, N-WASP and LOXL2 silenced pancreatic cancer cell which exhibited significant changes of fac- tors related to invasiveness and N-WASP expression. These findings suggest that N-WASP can be a target for the deter- mining of distant metastasis of pancreatic cancer.

Key words: N-WASP, EMT, pancreatic cancer, Snail, LOXL2

Legal entity responsible for the study: Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea, Gangnam Severance Hospital, Yonsei University College of Medicine

Disclosure: All authors have declared no conflicts of interest.

Funding: None

References

1. Takayori Y, Okamoto S, Hironaka Y, Homma H, Eto R, Nakashiro T, Kiyota T, Takahashi A, Hara H, Najima T, Morinaka I, Miki T, Suda T, Nomura S, Fuji K, Shitara A, Ohshu T, Yoshino T. Gastrointestinal and Medical Oncology, National Kyushu Cancer Center, Fukuoka, Japan, 12. Medical Oncology, Kyorin University Faculty of Medicine, Tokyo, Japan, 13. Biobank Translational Research Support Section, Translational Research Management Division, Clinical Research Support Office, National Cancer Center Hospital East, Kashiwa, Japan, 14. Clinical Trial Promotion Department, Chiba Cancer Center, Chiba, Japan, 15. Gastrointestinal Medical Oncology Division, National Cancer Center Hospital, Tokyo, Japan, 16. Division of Medical Oncology, Kanazawa University, Kanazawa, Japan, 17. Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, 18. Gastrointestinal Medical Oncology, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan, 19. Frontier Science for Cancer and Chemotherapy, Osaka University Graduate School of Medicine, Suita, Japan, 20. Medical Oncology, Kindai University Faculty of Medicine, Osaka, Japan, 21. Division of Cancer Center, Hokkaido University Hospital, Sapporo, Japan, 22. Gastroenterology, Satsuma Cancer Center, Satsuma, Japan, 23. Medical Oncology, Kyorin University Faculty of Medicine, Mitaka, Tokyo, Japan, 24. Faculty of Medicine, Division of Gastroenterology, University of Tsukuba, Tsukuba, Japan, 25. Clinical Research Support Office, National Cancer Center Hospital East, Kashiwa, Japan, 26. Pathology Division, Research Center for Innovative Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: We have conducted the Nationwide Cancer Genome Screening Project in Japan since April 2015 using Next Generation Sequencing in advanced non-colon gastrointestinal (GI) cancer (aNon-CRC), called as the SCRAM-Japan GI-SCREEN.

Methods: This study is ongoing with 20 major cancer centers. Patients with aNon-CRC, including who plan to or receive chemotherapy were eligible. DNA and RNA were extracted from FFPE tumor samples and were analyzed by the Oncomine Cancer Research Panel (OCP) which allows to detect gene mutations, copy number variants (CNVs) and gene fusions across 143 genes in a CLIA certified CAP accredited labor- tory. The detected genomic variant data were classified according to genetic drivers of cancer including gain- and loss-of-function or single nucleotide variant based on the Oncomine Knowledgebase. In this presentation, we show the results of advanced small intestine cancer cohort.

Results: As of October 31st in 2016, a total of 36 advanced small intestine cancer sam- ples were analyzed. The sequence was successfully performed in 26 tumors (72.2%). Out of 26 patients, the primary tumors are located in duodenum (n = 15), jejunum (n = 7), and ileum (n = 2), and unknown (n = 2). The frequently detected mutations in 26 samples of which results were available were KRAS (50.0%), TP53 (42.3%), and APC (23.1%). The frequently detected CNVs (> 7 copies) were MET/2 (77.6%) and CDK6 (3.8%). PIK3CA mutations were identified in 4 cases (15.4%) and BRCA mutations were identified in 2 cases (7.7%). No gene fusion was detected.

Conclusions: This nationwide screening system is efficient to detect rare gene alter- ations in advanced small intestine cancer. This novel knowledge provides an intriguing background to investigate new target-approaches and represents a progress toward more precision medicine.

Clinical trial identification: UMIN000016344

Legal entity responsible for the study: SCRAM-Japan GI-SCREEN

Funding: 15. SCRAM-Japan collaborating pharmaceutical companies, AMED, NCC

Disclosure: W. Okamoto: Research Funding from MSD. Y. Homma: Honoraria from Tenjin pharma. Speakers’ bureau from Taiho, Nikon kayaku, Daiichi sanyo and Novartis. Research funding from Daiichi Sankyo, Astrazeneca, Merck serono, Novartis and Teijin pharma. T. Kudo: Research funding from Yakult Honsha, Chugai Pharma and Ono Pharma. Y. Kumasawa: Honoraria from Novartis, Pfizer and Bayer. Speakers’ bureau from Taiho, Lilly, Chugai, Merck, Novartis, Pfizer, & Bayer. Research funding from Taiho, Lilly, MSD, Ono, Novartis, Bayer, Chugai and Yakult. H. Hara: Honoraria from Chugai, Taiho, Merck Serono, Yakult and Lilly Consulting or advisory role from Ono and Chugai. Research funding from AstaZeneca, Chugai, Merck Serono, MSD, Ono, Taiho, Takeda, Boehringer Ingelheim, Daiichi Sankyo, Lilly, etc. D. Naruge: Research funding from Taiho, Ono, Onco Therapy Science, Merck, Zeria, Lilly, Takeda, Chugai, Bayer, Grasso Smith Kline, Yakult, Sumitomo Danippon, Daiichi Sankyo, Novartis, Bristol-Myers Squibb, T. Moriwaki: Honoraria from Bayer, Chugai Pharma, Merck Serono, Novelpharma, Taiho Pharmaceutical, Takeda, and Yakult Honsha. Research funding from Boehinger Ingelheim, Chugai Pharma, MSD Oncology, Oncotherapy, Daiichi Sankyo, Takeda, and Yakult Honsha. S. Nomura: An immediate family member has been em- ployed by Asahi-Kasei pharma. K. Shutara: Receipt of grant/research supports from Daichi Sankyo, Chugai Pharma, Lilly, MSD, Taiho Pharmaceutical and Danippon, Sumitomo Pharma. A. Ohshu: An immediate family member has been employed by Celgene. Research funding from Bristol-Myers Squibb. T. Yoshino: Research funding from GlassSmithKline K.K. and Boehringer Ingelheim GmbH. All other authors have declared no conflicts of interest.

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The nationwide cancer genome screening project in Japan SCRAM- Japan GI-SCREEN: Efficient identification of cancer driver mutations in advanced small intestine cancer


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Background: We have conducted the Nationwide Cancer Genome Screening Project in Japan since April 2015 using Next Generation Sequencing in advanced non-colon gastrointestinal (GI) cancer (aNon-CRC), called as the SCRAM-Japan GI-SCREEN.

Methods: This study is ongoing with 20 major cancer centers. Patients with aNon-CRC, including who plan to or receive chemotherapy were eligible. DNA and RNA were extracted from FFPE tumor samples and were analyzed by the Oncomine Cancer Research Panel (OCP) which allows to detect gene mutations, copy number variants (CNVs) and gene fusions across 143 genes in a CLIA certified CAP accredited labor- tory. The detected genomic variant data were classified according to genetic drivers of cancer including gain- and loss-of-function or single nucleotide variant based on the Oncomine Knowledgebase. In this presentation, we show the results of advanced small intestine cancer cohort.

Results: As of October 31st in 2016, a total of 36 advanced small intestine cancer sam- ples were analyzed. The sequence was successfully performed in 26 tumors (72.2%). Out of 26 patients, the primary tumors are located in duodenum (n = 15), jejunum (n = 7), and ileum (n = 2), and unknown (n = 2). The frequently detected mutations in 26 samples of which results were available were KRAS (50.0%), TP53 (42.3%), and APC (23.1%). The frequently detected CNVs (> 7 copies) were MET/2 (77.6%) and CDK6 (3.8%). PIK3CA mutations were identified in 4 cases (15.4%) and BRCA mutations were identified in 2 cases (7.7%). No gene fusion was detected.

Conclusions: This nationwide screening system is efficient to detect rare gene alter- ations in advanced small intestine cancer. This novel knowledge provides an intriguing background to investigate new target-approaches and represents a progress toward more precision medicine.
Background: Peritoneal metastasis (PM) is detected synchronously in ~30% of patients with advanced gastric cancer (AGC), which has been considered as late stage of the disease with a poor prognosis and were generally treated with systemic chemotherapeutic or best supportive care. Two new surgical modalities that have evolved to treat these patients are cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). Our and other published retrospective data suggested that CRS plus HIPEC may prolong overall survival of the patients with limited PM. Still, the solid evidences based on large randomized clinical trials (RCT) are lacking. Accordingly, the present trial was initiated to define a comprehensive treatment.

Trial design: The investigator-initiated, multicenter, prospective two-arm RCT is comparing efficacy of CRS followed by HIPEC (CRS+HIPEC) versus chemotherapy (5-Fu based regimen, Chemo) alone for the treatment of AGC with limited PM. Eligibility for the trial is given in cT3-4aNxM1 (M1 limited to peritoneum, PCI score < 20 evaluated by diagnostic laparoscopy/MAC). The trial will recruit 220 participants who are 1:1 randomized to one of two arms after diagnostic laparoscopy. Participants enrolled in the Chemotherapy arm will receive standard chemotherapy according to the NCCN guideline. The CRS+HIPEC study arm will receive D2 gastrectomy plus peritonectomy plus HIPEC followed by systemic chemotherapy. The primary endpoint of the trial is overall survival. The secondary endpoints include progression-free survival, morbidity and mortality and quality of life. Biological substudies on biomarkers are included. Current status: The trial was approved by the Ethical Committee of Nanfang hospital, Southern Medical University, Guangzhou, China. Patient recruitment has begun in January 2017. Overall 12 Chinese sites will commence recruitment in 2017.

Clinical trial identification: NCT03024316

Legal entity responsible for the study: Nanfang hospital, Southern Medical University

Funding: None

Disclosure: All authors have declared no conflicts of interest.
A feasibility study of TAS-118 plus oxaliplatin as periphereal blood monocytes and neutrophils as determinant of treatment outcome in patients with previously treated advanced gastric adenocarcinoma.

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Background: TAS-118 is a novel combination antitumor agent, which the components of S, i.e. tegafur (FT), gimeracil (CDHP), and oteracil potassium (Oxo), are combined with calcium folinate (LV) into one granular form. In a phase II study, S-1 showed response to chemotherapy resulting in an improved disease control, improved survival and quality of life (QoL). In the ASCO-02 phase III trial, gemcitabine combined with cisplatin compared with gemcitabine alone prolonged PFS (8.0 vs. 5.0 mo) and OS (11.7 vs. 8.1 mo) and is considered as standard of care. So far this regimen has not been compared with other active combination regimen. Irinotecan in combination with 5-FU showed promising results in 1st- and 2nd-line therapy in many GI cancers. In pancreatic adenocarcinomas, the combination of liposomal irinotecan (niriu-118) plus LV improves survival in a phase I/II study. Our research hypothesis is that this regimen compares well with respect to clinical endpoints with the standard of care gemcitabine plus cisplatin in patients with advanced CCC.

Trial design: NICE is a randomized study for patients to be enrolled (n = 92) with locally advanced or metastatic, non-resectable, adenocarcinoma of the biliary tract: Arm A (experimental): Nal-IRI 80 mg/m2, leucovorin 400 mg/m2, 5-FU 2400 mg/m2 on day 1, cycle q2w, Arm B (standard): Cisplatin 25 mg/m2 and Gemicabine 1000 mg/m2 on day 1 and 8, cycle q4w. NIFE is an open label, non-comparative, multicenter, two-sided phase II study with an uncontrolled analysis of the results in both arms against a fixed PFS rate (< 40% at 6 months). The randomization (1:1) is to achieve two comparable patient groups. Primary objective is PFS at 6 months. Key secondary objectives are 3-year OS, PFS, ORR, DCR and QoL/TUDD. There will be a retrospective central surgical and radiological review. Tissue and blood sample collection will be mandatory for biomarker analyses (microdissection and exome sequencing of tumor tissue, cDNA exome sequencing, transcriptome, miRNA-arrays). Start was in 1/2017 to 25 centers in Germany.

Clinical trial identification: NCT03044587, January 23, 2017
Legal entity responsible for the study: AIO Studien gGmbH
Funding: Baxalta/She.

Disclosure: T J Ettrich: The Trial is sponsored by Baxalta/Shire. Thomas Ettrich was member of an Baxalta/Shire advisory board in 2016. All other authors have declared no conflicts of interest.

7717IP A phase 1/2 study of ramucirumab plus nivolumab in patients with previously treated advanced gastric adenocarcinoma.

H Shiigi1, H Miyamoto2, H Hara3, D Takahara4, N Machida5, T Esaki6, K Nagashima7, K Aoki8, K Honda9, Y Nagata10, T Miyamoto11, N Boku12, K Kato13
1Gastrointestinal Medical Oncology Division, National Cancer Center Hospital, Tokyo, Japan, 2Takeda, Chugai, Taiho, Merck Serono, Research funding: Chugai, Taiho, Merck Serono, Gilead, D. Takahara: Research funding: Taiho Honorary: Taiho, Yakult, Lilly, Chugui, N. Ishizuka: Stock ownership: Shionogi, Honoraria: Taiho, Lilly, Chugui, Kyowa Hakko Kirin, Eisai, Sato, Taiwa, Takada, Bristol- Myers Squibb, Ono, Bayer, Daisan Sumitomo, Research funding: Ono, Pharmaceutical and Yakult. Advisory Role from Lilly Japan, Taiho, Pfizer, Bayer, Sanofi, Ono, Daiichi Sankyo. T. E. Nakajima: Honoraria: Eisai, Astellas, Taiho, Bayer, Daiichi-Sankyo, Pfizer, AstraZeneca, Merck Serono, Sanofi, Novartis, Ono, Bristol-Meyers, MSD, Research funding: Eisai, Chugai, MSD, Lilly, Astereza, Novartis, Taiho, Bayer, Astellas, Ono, Daiichi Sankyo. T. Ishizuka: Honoraria: Taiho, Chugui, Yakult, Lilly, Eisai, Ethison, Covidien. N. Boku: Honoraria: Taiho, Lilly, Chugui, Ono, Merck-Serono, Yakult. Research funding: Ono, Bristol- Myers Squibb, Taiho, K. Yamauchi: Speaker’s bureau: Takeda, Lilly, Taiho, Shionogi, Ono, Merck, Research funding: Yakult, Taiho, MSD, Ono, Chugui, Lilly, Merck. All other authors have declared no conflicts of interest.

Clinical trial identification: UMIN00024088, release date: 5 Dec 2016
Legal entity responsible for the study: Kenji Yamaguchi
Funding: Taiho, Yakult

Acil ("DCF regimen") every 3 weeks has been shown to improve efficacy of 1st-line trt in S. Manfredi 19, J. Taieb 20 pare FOLFOX to TFOX in 1st line trt of advanced gastric cancer. less toxic as compared DCF regimen. The aim of this current phase III study is to com-

A. Zaanan 1, E. Samulin 2, C. Louvet 3, C. Montémyard 4, F. Khermissa 5, D. Bauche 6, A. Lecuyer 7, F. Chiringhelli 8, P. Bernard 9, T. Etsaki-Honorat 10, Chagui, Eli Lilly, Taib, Merck Serono, Ono, Nilon Kayakou, Esaï, Research Funding; Eli Lilly, Taibo, Novartis, Daichi-Sankyo, DS Pharma, AstraZeneca, Merck Serono, Ono, MSD, N. Boku, K. Kato, Consultant, Advisory Board; Ono. Research Funding; MSD, N. MSd. All other authors have declared no conflicts of interest.

Table: 773TIP

<table>
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<th>FOFOX (BRAS A)</th>
<th>TFOX (BRAS B)</th>
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<tr>
<td>Folinic acid (D1)</td>
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</tr>
<tr>
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<tr>
<td>SFL bolus (D1)</td>
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<tr>
<td>SFL continu (D1-2)</td>
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<tr>
<td>Docetaxel (D1)</td>
<td>50 mg/m²</td>
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Tri has to be administrated until disease progression or unacceptable toxicity. The pri-

rate, therapeutic index, toxicity, time to final deterioration in quality of life. Stratification factors are: centre, WHO PS, adjuvant chemotherapy or radio-che-

tary, tumour stage, primary tumour location and pathological subtype. 17 patients have been randomized over the 506 planned since 19/12/2016.

Clinical trial identification: NCT02715804

Trial design: 420 patients ≥18 years with untreated HA-High metastatic PDA, ECOG PS-0 are randomized (stratified by North America/Europe/Other) 2:1 to NAB 125 mg/m² + GEM 1000 mg/m² + PEGPH2O 3.0 g/kg or to NAB + GEM = placebo, respectively. Patients with HA-High tumour who are prospectively identified by the co-
developed VENTANA HA RxDx Assay, which identifies HA in the extracellular matrix. HA-High status (indicating patients who may achieve clinical benefit) was determined by Halozyme to be ≥50% HA staining based on clinical outcome data from a Phase 2 study. Treatment is provided in 4-week cycles (Wk 1-3, Wk 4 rest) until disease pro-
gression, unacceptable toxicity, death, or consent withdrawal. PEGPH20 or placebo is given twice weekly (Cycle 1) then weekly (Cycles 2-4), NAB + GEM once weekly for all cycles. Dexamethasone is given before and after PEGPH20 to reduce treatment-related musculoskeletal symptoms and enoxaparin is given to minimize thromboembolic events. Tumor response will be assessed by an independent central imaging vendor using RECIST v1.1. Adverse events will be graded per NCI CTCAE v4.03. An independ-
ent Data Monitoring Committee will evaluate safety and efficacy (PSF and OS) data. Trial initiated Q1/2016 (EudraCT 2015-004068-13; NCT02715804).

Clinical trial identification: NCT02715804

Legal entity responsible for the study: Halozyme Therapeutics, Inc.

Funding: Halozyme Therapeutics, Inc.


Legal entity responsible for the study: FFCF

Funding: None

Disclosure: A. Zaanan: Consulting and/or advisory board for Roche, Merck Serono, Amgen, Sanofi, Lilly. E. Samalin: Personal grants for consultancy for Sanofi, Lilly, Novartis, Bayer, Roche, Ipsen, Amgen, Merck. F. Khermissa: Personal grants for consult-
ancy for Sanofi, Roche, Ipsen, Bayer. O. Bouché: Personal grants for consultancy for Roche, Merck, Amgen, Lilly, Novartis Oncology. F. Ghringhelli: Personal grants for consultancy for Amgen and Merck. B. Chibaudel: Consulting: Sanofi, Lilly. Honoraria: Bayer, Kepheren, Kantar H. Travels: Roche, Sanofi, Amgen, Merck, Lilly. Y. Molin: Regional board for Janssen. O. Romano: Roche, Pierre Fabre, Sanofi. T. Aparicio: Personal grants for consultancy for Sanofi, Roche, Baxalta, Celgene, Lilly, Merck, Med, Pfizer, Roche, Sanofi, Abbvie. All other authors have declared no conflicts of interest.
Background: Sorafenib is the standard of care (SOC) for first-line HCC; however, there is no clear SOC after disease progression or intolerance to sorafenib. Because most HCC is driven by inflammation, the rationale to evaluate immunotherapy in patients (pts) with this type of cancer is strong. The randomized, double-blind, placebo-controlled phase 3 KEYNOTE-240 study (ClinicalTrials.gov, NCT02702401) was designed to compare efficacy and safety of the anti–PD-1 antibody pembro vs placebo in pts with previously treated advanced HCC.

Trial design: Pts aged ≥ 18 years with histologically or cytologically confirmed HCC (fibrolamellar and mixed hepatocellular/cholangiocarcinoma subtypes excluded), documented progression after stopping treatment with sorafenib or intolerance to sorafenib, no previous systemic therapy for HCC other than sorafenib, disease not amenable to a curative treatment approach (eg, transplantation, surgery, or ablation), measurable disease confirmed by central imaging vendor review per RECIST v1.1, Child-Pugh liver score A, ECOG performance status 0-1, adequate organ function, and predicted life expectancy > 3 months are eligible. Pts will be randomly assigned 2:1 to receive pembrolizumab 200 mg IV Q3W + placebo Q3W + BSC for up to 35 cycles (~2 years) or until disease progression, unacceptable toxicity, or investigator decision. Randomization will be stratified by geographic region, presence of macrovascular invasion, and tumor type.

Primary endpoints include objective response rate and disease control rate assessed by investigator local treatment practice. Response will be assessed per QEW/RECIST v1.1 by central imaging vendor review. Adverse events (AEs) will be assessed throughout treatment and for 30 days thereafter (90 days for serious AEs) and graded per NCI CTCAE v4.0. Primary objectives are comparison of PFS per RECIST v1.1 by central imaging vendor review and OS between treatment arms. Secondary objectives are comparison of ORR, DOR, DCR, and TTP per RECIST v1.1 by central imaging vendor review, and evaluation of safety and tolerability. Planned enrollment in KEYNOTE-240 is 488 pts across 26 countries.


Legal entity responsible for the study: Merck & Co., Inc., Kenilworth, New Jersey, USA

Funding: Merck & Co., Inc., Kenilworth, New Jersey, USA

Patients underwent B0 and D2 gastrectomy and pathology diagnosed > T4a or positive lymph node (N+) disease per AJCC 7-th edition were enrolled in this study. Eligible patients were randomly assigned to receive adjuvant chemotherapy of SOX regimen and concurrent 3D-CRT/IMRT (50.4 GY/28) or six cycles of SOX alone. Block randomization was done and stratified by disease stage. Primary endpoints are disease-free survival (DFS). Secondary endpoints are overall survival (OS), local control rate (LCR) and toxicity.

Clinical trial identification: ChiCTR-TRC-12029219
Legal entity responsible for the study: N/A
Funding: None
Disclosure: All authors have declared no conflicts of interest.

777TIP

Impact of early palliative care on overall survival of patients with metastatic upper gastrointestinal cancers treated with first-line chemotherapy: Phase III EPIC trial
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Background: Palliative care (PC) has usually been offered at end-life stage, although the World Health Organization recommends providing PC as early as possible in the course of malignancies. Temel et al. (N Engl J Med 2010) have shown that early PC (EPC) provides a favorable effect on quality of life, as well as a surprising benefit on overall survival (OS) (secondary endpoint of this trial) over standard treatment to patients (pts) with metastatic lung cancer. Median OS of pts with metastatic upper gastrointestinal cancers does not exceed 10-11 months, which is as poor as that reported with metastatic lung cancers. Whether or not OS benefit with EPC also applies to pts with metastatic upper GI cancers is unknown. Demonstration of such benefit in these pts would lead to an earlier integration of PC in oncologic care.

Trial design: EPIC is a randomized phase III trial. It is aimed to estimate the OS benefit of EPC combined with standard oncologic care over standard oncology care only, in pts with metastatic upper GI cancers who start 1st-line chemotherapy. Eligibility criteria also include ECOG PS 0-2 and life expectancy > 4 weeks. Main exclusions criteria include: locally advanced tumors, esogastic cancers with unknown or positive HER2 status, dysphagia, and jaundice. Treatments will be randomized in a 1:1 ratio; a minimization procedure will be used to balance pts according to center, PS (0-1 vs 2) and tumor location (esogastic/gastric cancers, pancreas, and bilar tract). Pts will be recruited from 40 hospitals. The study includes a phase II dose finding study to determine the best dose of EPC for pts with metastatic upper GI cancers and 1st-line chemotherapy.

Clinical trial identification: NCT02833474
Legal entity responsible for the study: Centre Oscar Lambret
Funding: None
Disclosure: All authors have declared no conflicts of interest.

781TIP

Apatinib and irinotecan combination treatment in first-line chemotherapy refractory esophageal squamous cell carcinoma: A phase I dose escalation study
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Background: Esophageal cancer is one of the common malignant tumors. Different from that in western countries, esophageal squamous cell carcinoma (ESCC) is still the dominant pathological type in China and account for more than 95% of cases in clinic. The annual incidence of esophageal squamous cell carcinoma is 260,000 with the mortality of 210,000 in China. For patients with recurrent or metastatic disease, chemotherapy is one of important treatment alone or with radiotherapy. Taxane, platinum, and fluoropyrimidine have been reported effective in ESCC, and are popularly used in first line treatment of ESCC. However, there is still no standard 2nd-line treatment for ESCC patients. Apatinib, also known as TY98681, is an oral tyrosine kinase inhibitor to vascular endothelial growth factor (VEGFR) receptor, by which blocks the VEGF signaling pathway and results in anti-angiogenesis of tumors. Preclinical data has shown that it is effective in the treatment of a variety of solid tumors including esophageal cancer. And it was approved and launched in China in 2015 as a 3rd line treatment for patients with advanced gastric cancer. However, the role of anti-angiogenes targeting treatment including apatinib is unknown. Here, we initialize a dose escalation phase I study to identify the dosage of apatinib when combined with irinotecan to treat ESCC patients who were with recurrent disease after esophagectomy and refractory to 1st-line chemotherapy.

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doi:10.1093/annonc/mdx369 | 167
Trial design: Patients, age 18-70, with measurable tumor lesion, failed in or progression after 1st line chemotherapy, were enrolled in this 3 + 3 design study. Apatinib dosage escalated from 250 mg, 300mg, to 750 mg daily in 3 different cohorts while the dosage of trastuzumab was maintained at 150mg/m² every 2 weeks for 3 cycles (6 weeks). The dose-limiting toxicity (DLT) was identified as grade 4 hematologic toxicity and grade 3 to 4 non-hematologic toxicity according to NCI CTCAE 4.0 criteria. The primary end point is the maximum tolerated dose (MTD) and the secondary end points include the objective response rate (ORR), progression-free survival (PFS) and overall survival (OS).

Clinical trial identification: NCT02645864

Legal entity responsible for the study: Dr. Xiaodong Zhang

Funding: HengRui Cancer Research Foundation of CSCCO (Y-HR-2015-030)

Disclosure: All authors have declared no conflicts of interest.

782TIP

PANOVA 3: A phase 3 study of TTFIELDS with gemcitabine and nab-paclitaxel for front-line treatment of locally-advanced pancreatic adenocarcinoma (LAPC)

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Background: TTFIELDS are a non-invasive, regional antimitotic treatment modality, which has been approved for the treatment of glioblastoma by the FDA. TTFIELDS predominantly act by disrupting the formation of the mitotic spindle during metaphase. TTFIELDS were effective in multiple preclinical and clinical models of pancreatic cancer. PANOVA was the first trial testing TTFIELDS in pancreatic cancer patients, demonstrating their safety when combined with gemcitabine and nab-paclitaxel, and preliminary promising efficacy in LAPC. PANOVA 3 is designed to test the efficacy of adding TTFIELDS to the same chemotherapy combination in this disease stage.

Trial design: Approximately 600 patients with unresectable, LAPC (per NCCN guidelines) will be enrolled in this prospective, randomized trial. Patients should have an ECOG score of 0-2 and no prior progression or treatment. Patients will be stratified based on their performance status and geographical region. Gemcitabine and nab-paclitaxel will be administered at standard dose. The NovoTTF-100L (150kHz) system will be used by experimental arm patients for at least 18 hours/day until local disease progression per RECIST Criteria V1.1. Follow up will be performed q8w, including a CT scan of the chest and abdomen. Following local disease progression, patients will be followed monthly for survival. Overall survival will be the primary endpoint and progression-free survival, objective response rate, rate of resectability, quality of life and toxicity will all be secondary endpoints.

Legal entity responsible for the study: Novocure

Funding: Novocure


1733PD

New promising combination therapy of a mitochondrial metabolism inhibitor with mFOLFOXIRINOX in pancreatic cancer

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Background: Stage IV pancreatic cancer is a lethal disease. Current standard practice is combination chemotherapy such as FOLFIRINOX or Gemcitabine and Abraxane. The glycolic and mitochondrial metabolism are aberrant in pancreatic cancer and translate into chemoresistance. Inhibition of glutamine metabolism can potentially synergize with therapies that increase intracellular reactive oxygen species such as FOLFIRINOX components. CPI-613 is a novel antimitochondrial developed by Rafael Pharmaceuticals that showed preclinical activity in pancreatic cancer.

Methods: We designed a phase 1 study to evaluate for synergy between CPI-613 and FOLFIRINOX for patients with stage IV pancreatic cancer. Aims: To determine the maximum tolerated dose (MTD) of CPI-613 and FOLFIRINOX for patients with stage IV pancreatic cancer. Aims: To determine the maximum tolerated dose (MTD) of CPI-613 when used in combination with modified FOLFIRINOX. To assess the safety of CPI-613 + modified FOLFIRINOX to obtain preliminary data on efficacy of treatment.

Results: Updated Results as of July, 2017 Toxicity: No deaths due to adverse events were reported. The MTD was identified at 500 mg/m² and a total of 18 patients were treated at the MTD. The most common grade 3-4 non-hematologic adverse events: hyperglycemia, hypokalemia, peripheral sensory neuropathy, diarrhea, and abdominal pain. The most common grade 3-4 hematologic adverse events: neutropenia, lymphopenia, anemia and thrombocytopenia Preliminary efficacy: Of the 18 patients treated at MTD – 8 patients are alive and 4 patients are still on treatment. The median PFS is 10.4 months, 95% CI (119 to 560 days) – 3 patients are still alive and on treatment who have not progressed. Median overall survival is 20.1 months, data still maturing. The 95% CI cannot be accurately estimated yet. Three patients achieved a complete response.

Conclusions: CPI-613 is a first in class non-redox active lipopeptide derivative being tested in phase I clinical trial in combination with FOLFIRINOX. The MTD for CPI-613 was identified at 500mg/m². The treatment combination is feasible and well-tolerated. The response rate was 61%, which is higher than gemcitabine-based regimens. The median PFS is 10.4months and the median OS is 20.1 months, data still maturing. A randomized, international phase 3 study of FOLFIRINOX vs. CPI613 will open in 2018.


Legal entity responsible for the study: Wake Forest University, School of Medicine

Funding: Cornerstone Pharmaceutical now Rafael Pharmaceuticals

Disclosure: T. Pardee: Chief Medical Officer and employee of Rafael Pharmaceutical (name change on June 5th 2017 from Cornerstone Pharmaceutical). Dr Pardee has no stock or equity in the company. S. Luther: Employee of Rafael Pharmaceuticals and the COO of the company. He owns stock in the company. All other authors have declared no conflicts of interest.

1734PD

Anti-CTGF human recombinant monoclonal antibody pamrevlumab increases resectability and resection rate when combined with gemcitabine/Nab-paclitaxel in the treatment of locally advanced pancreatic cancer patients

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Background: Pancreatic ductal adenocarcinomas (PDAC) exhibit a high degree of desmoplasia, with extensive connective tissue growth factor (CTGF) expression and extracellular matrix production1, 2. Pamrevlumab (FG-3019), anti-CTGF antibody, is being evaluated in phase I clinical trial in combination with FOLFIRINOX. The MTD for CPI-613 was identified at 500mg/m². The treatment combination is feasible and well-tolerated. The most common grade 3–4 non-hematological adverse events: hyperglycemia, hypokalemia, peripheral sensory neuropathy, diarrhea, and abdominal pain. The most common grade 3-4 hematologic adverse events: neutropenia, lymphopenia, anemia and thrombocytopenia Preliminary efficacy: Of the 18 patients treated at MTD – 8 patients are alive and 4 patients are still on treatment. The median PFS is 10.4 months, 95% CI (119 to 560 days) – 3 patients are still alive and on treatment who have not progressed. Median overall survival is 20.1 months, data still maturing. The 95% CI cannot be accurately estimated yet. Three patients achieved a complete response.

Conclusions: CPI-613 is a first in class non-redox active lipopeptide derivative being tested in phase I clinical trial in combination with FOLFIRINOX. The MTD for CPI-613 was identified at 500mg/m². The treatment combination is feasible and well-tolerated. The response rate was 61%, which is higher than gemcitabine-based regimens. The median PFS is 10.4months and the median OS is 20.1 months, data still maturing. A randomized, international phase 3 study of FOLFIRINOX vs. CPI613 will open in 2018.


Legal entity responsible for the study: Wake Forest University, School of Medicine

Funding: Cornerstone Pharmaceutical now Rafael Pharmaceuticals

Disclosure: T. Pardee: Chief Medical Officer and employee of Rafael Pharmaceutical (name change on June 5th 2017 from Cornerstone Pharmaceutical). Dr Pardee has no stock or equity in the company. S. Luther: Employee of Rafael Pharmaceuticals and the COO of the company. He owns stock in the company. All other authors have declared no conflicts of interest.
Background: In the LATITUDE study, treatment with ADT+AA significantly improved overall survival and delayed disease progression in pts with newly diagnosed, high-risk, metastatic castration-naïve prostate cancer (mNPC). In this analysis we evaluated the impact of ADT+AA on PROs, including symptom and health-related quality of life (HRQoL) measures.

Methods: 1199 mNPC pts were randomized 1:1 to ADT+AA+P or ADT+P (placebos (PBOs). Brief Pain Inventory-Short Form (BPI-SF), Brief Fatigue Inventory (BFI), Functional Assessment of Cancer Therapy-Prostate (FACT-P), and EQ-SD-5L questionnaires were administered at baseline (BL), Day 1 of Cycles (C) 2-13, then every 2 months until treatment discontinuation (TD). EQ-SD-SL were performed every 4 months until 12 months after TD. Time to event and repeated measures analyses on changes from baseline were conducted.

Results: Questionnaire compliance rate was high at ≥ 90%. Compared to ADT+PBOs, the ADT+AA+P arm had significant delays in time to pain and fatigue intensity and interference progression (Table). FACT-P assessments demonstrated significant delay in progression for the total score and symptom subscales for the ADT+AA+P arm (Table). Repeated measures analyses showed maintenance or improvement from BL for the ADT+AA+P arm compared to the ADT+PBOs arm, with significant differences emerging as early as C2. Significant improvement from BL in EQ-SD VAS for general health status and health utility scores occurred as early as C5 and was maintained throughout the study.

Conclusions: Compared to ADT+PBOs, treatment with ADT+AA+P consistently demonstrated improvement across multiple PRO measures, with statistically significant improvement in HRQoL and delays in progression of pain and fatigue intensity and interference, and functional decline. Results for PBOs were consistent with improvements in clinical outcomes.

Clinical trial identification: EudraCT: 2012-002940-26 NCT01715285

Legal entity responsible for the study: Janssen Research & Development

Funding: Janssen Research & Development


Table 7830 Time to Progression and Relative Risk for HRQoL End Points

<table>
<thead>
<tr>
<th>Measure</th>
<th>ADT+AA+P (months)</th>
<th>ADT+PBOs (months)</th>
<th>HR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to worst pain intensity progression (BPI-SF)</td>
<td>NR</td>
<td>16.6</td>
<td>0.695 (0.583-0.829)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median time to pain interference progression (BPI-SF)</td>
<td>NR</td>
<td>18.4</td>
<td>0.671 (0.561-0.803)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median time to fatigue intensity progression (BFI)</td>
<td>NR</td>
<td>NR</td>
<td>0.652 (0.527-0.805)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median time to fatigue interference progression (BFI)</td>
<td>NR</td>
<td>NR</td>
<td>0.594 (0.470-0.750)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median time to FACT-P degradation</td>
<td>Total Score</td>
<td></td>
<td>12.9</td>
<td>0.853 (0.736-0.989)</td>
</tr>
<tr>
<td></td>
<td>Pain-related Subscale</td>
<td>10.2</td>
<td>6.5</td>
<td>0.760 (0.659-0.876)</td>
</tr>
<tr>
<td></td>
<td>Prostate Cancer Subscale</td>
<td>8.3</td>
<td>5.6</td>
<td>0.808 (0.701-0.930)</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval.
Lutetium-177 PSMA (LuPSMA) theranostics phase II trial: Efficacy, safety and QoL in patients with castrate-resistant prostate cancer treated with LuPSMA

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Background: Progressive metastatic castrate-resistant prostate carcinoma (mCRPC) is a highly lethal condition. Lutetium-177 (177Lu)-PSMA617, a radiolabelled small molecule, binds with high affinity to prostate-specific membrane antigen (PSMA) enabling beta particle therapy targeted to mCRPC.

Methods: In this phase II prospective trial, 30 pts with PSMA-avid mCRPC who had failed standard therapies received up to 4 cycles of 177Lu-LuPSMA617 every 6 weeks. The primary endpoints were PSA and imaging response (PCWG2) and toxicity (CTCAE v4).

Results: All patients were enrolled between 10/2015 and 12/2016 (median age 69 yr, ECOG 1; PSA doubling time 2.2 months) with 3 pts awaiting a final treatment cycle. 87% received prior chemotherapy, 47% cabazitaxel and 83% prior abiraterone and/or enzalutamide. Median dose was 7.5 GBq (range 4.4 – 8.7 GBq) prospectively adjusted according tumour burden, renal function and weight. At this interim analysis, 17/30 pt (57%) achieved PSA decline > 50%, including 11/30 (37%) with decline > 80%. In 17 pt with soft tissue disease, objective response (RECIST PR + CR) occurred in 12 pt (71%). Most common adverse events were grade 1 xerostomia (19 pt, 63%) and nausea (15 pt, 50%). Grade 3 or higher hematotoxicity occurred in 5 pt (17%), all had baseline thrombocytopenia and were reversible. Following the first cycle of LuPSMA, global bone pain improved significantly (> 10 points) in 11/30 pt (37%), while in those with bone pain, mean severity score improved significantly (> 10 points) in 9/21 pt (43%).

Conclusions: The LuPSMA Phase II trial provides evidence of high response rates and low toxicity with improved QoL and pain reduction in men with mCRPC who have failed conventional therapies.


Legal entity responsible for the study: Peter MacCallum Cancer Centre, Melbourne, Australia


Disclosure: All authors have declared no conflicts of interest.

DNA repair gene panel mutations in young onset and aggressive vs non aggressive prostate cancer cases in the UK

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Background: Prostate cancer (PrCa) is the most common solid tumour in men in the Western world. There is evidence that PrCa predisposition is due to germline common and rare variation.

Methods: We sequenced 175 genes in the DNA damage response and repair pathways using an Agilent custom capture kit and Illumina technology in PrCa cases diagnosed at < 65 years compared with controls in the UK (mean coverage 76X). Data were analysed from 1346 PrCa cases and 1186 controls using a GATK 2.8 analysis pipeline.

Results: We identified 51 single nucleotide variants (SNVs) and 172 indels; 216 unique protein truncating variants (PTVs) were in 96 genes of the 175 gene panel. The total number of PTVs in cases was significantly higher (181) than in controls (122); in particular, in the BROCA gene set of 22 tumour suppressor genes (P = 0.002). Mutations in BRCA1, BRCA2, ATM, MSH5 and CHEK2 were 3 times more common in cases compared with controls (P = 0.0018). To investigate if aggressive cases had a different mutation burden we compared 204 aggressive (Gleason score > 8) versus 1049 non-aggressive (Gleason score ≤ 7) cases. In the single variant analysis, one variant in BRCA2, rs28897754 ( rs295899) showed association with a more aggressive phenotype (P = 0.0016). Gene burden testing showed BRCA2, MSH5, PALB2 and CHEK2 had an OR > 3 in aggressive v non aggressive cases (14% v 4% respectively). Men who died of PrCa had a 17% incidence of mutation in a subset of the 175 gene panel.

Conclusions: We have shown that there is a higher percentage of DNA damage response and repair gene germline mutations in PrCa cases occurring at < 65 years, in those with aggressive and lethal disease and this result will enable us to develop a testing panel for use in clinical care in the near future.

Clinical trial identification: UKGCP5 - CCR0486 & 06MR0202/4

Legal entity responsible for the study: The Institute of Cancer Research

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Prognostic associations of prostate-specific antigen (PSA) decline with survival, radiographic response and progression in chemotherapy-naïve men with metastatic castration-resistant prostate cancer (mCRPC) treated with enzalutamide

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Background: In the PREVAIL clinical trial, enzalutamide provided significant improvements vs placebo in radiographic progression-free survival (rPFS) and overall survival (OS) in chemotherapy-naïve men with mCRPC. This post hoc analysis aimed to evaluate the prognostic association between the magnitude of PSA decline from baseline and clinical outcomes in PREVAIL.

Methods: Men from the enzalutamide and placebo arms of PREVAIL were grouped into categories of confirmed maximal PSA decline from baseline at month 3 of

Table: 784O

<table>
<thead>
<tr>
<th>PSA-PFS (months)</th>
<th>AS + D (n = 125)</th>
<th>AS alone (n = 125)</th>
<th>HR (95%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>85.2 (9.2-21.5)</td>
<td>18.6 (17.6-20.2)</td>
<td>0.85 (0.62-1.16)</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>8.8 (7.7-10.2)</td>
<td>9.7 (6.9-10.9)</td>
<td>1.01 (0.72-1.40)</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>8.3</td>
<td>8.1</td>
<td>1.16 (0.76-1.77)</td>
<td>0.49</td>
<td></td>
</tr>
</tbody>
</table>

785PD

787PD

Annals of Oncology
Abbreviations: CI, confidence interval; CR, complete response; HR, hazard ratio; mo, months; NYR, not yet reached; OS, overall survival; PR, partial response; PSA, prostate-specific antigen; ref, reference, rPFS, radiographic progression-free survival.

Clinical trial identification:

Table 788PD

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Maximal PSA Decline From Baseline at Month 3 in the Enzalutamide Arm (N = 872)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Decline/ Decline &lt; 30% (n = 94/872)</td>
</tr>
<tr>
<td>Best objective soft-tissue response (CR or PR), % (95% CI)</td>
<td>12.0 (4.5-24.3)</td>
</tr>
<tr>
<td>Median (95% CI) time to PSA progression, mo</td>
<td>3.7 (3.7-4.6)</td>
</tr>
<tr>
<td>Median (95% CI) rPFS, mo</td>
<td>7.9 (3.7-NYR)</td>
</tr>
<tr>
<td>HR (95% CI) for rPFS</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>Median (95% CI) OS, mo</td>
<td>23.1 (17.8-28.0)</td>
</tr>
<tr>
<td>HR (95% CI) for OS</td>
<td>1.0 (ref)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CR, complete response; HR, hazard ratio; mo, months, NYR, not yet reached; OS, overall survival; PR, partial response; PSA, prostate-specific antigen; ref, reference, rPFS, radiographic progression-free survival.

Introduction

Patients and Methods

Results: In PREVAIL, men were randomized to enzalutamide (n = 872) or placebo (n = 843). Most men in the placebo arm (66%, 558/845) had no PSA decline/decline < 30%, in contrast to 11% (94/872) in the enzalutamide arm. In the enzalutamide arm, 81% (701/872) of men had a PSA decline of ≥ 50% from baseline at week 13, 73% (639/872) had a PSA decline of ≥ 50% and 30% (307/872) had a PSA decline of ≥ 90%. Key outcomes for the enzalutamide arm are provided by PSA decline category in the Table. PSA flare (rise followed by a fall) after 3 months was rare with enzalutamide (< 1%). Conclusions: PSA declines after 3 months of enzalutamide therapy are strongly associated with soft-tissue response and improvements in rPFS and OS. Providing updated prognostic information to chemotherapy-naive men with mCRPC can be of clinical value given the heterogeneity of long-term outcomes.

Clinical trial identification: NCT01212991

Legal entity responsible for the study: This study was sponsored by Medivation, Inc. (which was acquired by Pfizer, Inc. in September 2016) and Astellas Pharma, Inc., the co-developers of enzalutamide.

Funding: This study was sponsored by Medivation, Inc., (which was acquired by Pfizer, Inc. in September 2016) and Astellas Pharma, Inc., the co-developers of enzalutamide.


788PD

Randomized controlled trial comparing radiotherapy +/- endocrine therapy versus endocrine therapy alone for PSA failure after radical prostatectomy: Japan Clinical Oncology Group Study JCGOG401

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Background: A standard therapy has not been established on PSA failure after radical prostatectomy for localized prostate cancer. Therefore, the randomized controlled trial was designed to confirm the superiority of radiotherapy ± endocrine therapy over endocrine therapy alone for PSA failure after radical prostatectomy.

Methods: Patients were randomly assigned to arm A (endocrine therapy only: bicalutamide (BCL) monotherapy followed by LHRH agonist in case of BCL failure), or arm B (64.8 Gy of salvage radiotherapy (SRT) followed by same regimen of arm A in case of treatment failure of SRT). The primary endpoint is time to treatment failure (TTF) of BCL, and secondary endpoints are TTF of protocol treatment, clinical relapse-free survival (RFS), overall survival (OS), adverse events. The planned sample size was 210 to detect improvement of median TTF of BCL from 5 years to 8.3 years with one-sided alpha of 0.05 and power of 80%. This trial is registered with UMIN-CTR (C000000026).

Results: A total of 210 patients (105 patients in each arm) were registered from May 2004 to May 2011. The TTF of BCL was significantly better in arm B as shown in Table 1 (Hazard ratio 0.56 90% CI (0.40–0.77), one-sided p = 0.001). The 33 patients (32%) of 102 patients with SRT of arm B had no treatment failure of SRT, resulting in being free from hormonal therapy. In addition, TTF of protocol treatment was also significantly better in arm B. However, clinical RFS and OS were similar between the arms. Grade 4 adverse event was reported in one patient in arm B.

Conclusions: The first SRT had advantage in both TTF of BCL and protocol treatment. Although the clinical outcomes of both arms of salvage therapy were similar with each other in terms of clinical PFS and OS, the SRT was effective in case of the patients, which contributed to avoid the salvage endocrine therapy.

Clinical trial identification: UMIN-CTR (C000000026)

Legal entity responsible for the study: Japan Clinical Oncology Group, JCOG

Funding: Ministry of Health, Labor and Welfare of Japan


Advisory fee from Ono Pharma Inc. and Takeda Pharma. S. Naito: Personal financial interest from Astellas Pharma Inc., Takeda Pharmaceutical Co., Ltd. and Green Annals of Oncology abstracts

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Aibiraterone acetate (AA) + prednisolone (P) for metastatic castration-resistant prostate cancer (mCRPC) with early progression or non-response to androgen deprivation therapy (ADT)

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Background: mCRPC with early progression (≤1 year) or non-response to initial ADT carries a poor prognosis, and there is no consensus regarding second-line therapy for these patients (pts) [ADT poor responders]. Although AA + P is effective for chemonaive mCRPC, limited data is available for ADT poor responders; thus, we conducted this study to evaluate the efficacy and safety of AA + P as secondary treatment for this population.

Methods: This was a multicenter, open-label, single-arm, 2-stage trial according to Simon’s minmax design [hypothesis: p0 = 0.150, p1 = 0.350, α = 0.025, β = 0.100], and 48 pts were required to efficacy analysis. Key eligibility: Chemo-naive mCRPC (testosterone level < 50 ng/dL, under medical/surgical castration), age ≥ 20, and evidence of prostate specific antigen (PSA) progression by PCWG2 criteria ≤ 1 year or without achieving a normal PSA level (< 4 ng/mL) during initial ADT. For eligible pts, 1000 mg AA with 10 mg P was administered until disease progression. The primary endpoint was the proportion of patients achieving a PSA decline of ≥ 50% from baseline after 12 weeks of treatment in accordance with PCWG2 criteria (PSA response rate).

Results: Fifty pts were enrolled and 49 were evaluable for efficacy analysis. At baseline, the median age was 73 (range 55–86), the median PSA level was 28.34 mg/mL (2.28–294.25), and the median duration of initial ADT was 6.4 months (1.4–18.8). Among the patients, 90.0% had a total Gleason score 8, and all had a treatment history of ≥8 cycles of chemotherapy. Most patients showed high treatment compliance (>95% with AA [n = 47/50, 94.0%] and P [n = 46/50, 92.0%]). PSA response rate was 55.1% (n = 27/49; 95% CI 41.3–68.1), and the PSA decline began after 4 or 8 weeks from baseline. The treatment was well tolerated with <25% of grade ≥ 3 adverse events.

Conclusions: This is the first study to investigate the efficacy of AA + P for ADT poor responders. The study demonstrated similar efficacy to the Phase 3 study COU-AA-302, which further supports the efficacy of AA + P for ADT poor responders. AA + P appears to be a promising treatment for initial ADT poor responders with an acceptable safety profile. This study is ongoing as follow up on time to PSA progression.

Clinical trial identification: NCT02403858 (March 27, 2015).

Legal entity responsible for the study: Janssen Pharmaceutical K.K.

Funding: Janssen Pharmaceutical K.K.


Table: 789PD

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<th>5-year TTF of BCL</th>
<th>Arm A (endocrine therapy only) (%)</th>
<th>95% CI</th>
<th>Arm B (radiation +/- endocrine therapy) (%)</th>
<th>Hazard Ratio (95% CI)</th>
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<tr>
<td>57.0% (46.7%–66.0%)</td>
<td>69.7% (59.6%–77.7%)</td>
<td>0.56 (0.38-0.82)</td>
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<td>67.0% (56.9%–75.3%)</td>
<td>76.8% (67.1%–83.9%)</td>
<td>0.66 (0.44-1.00)</td>
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<td>93.8% (88.6%–97.2%)</td>
<td>88.9% (80.9%–93.7%)</td>
<td>0.90 (0.45-1.81)</td>
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<td>99.0% (93.4%–99.9%)</td>
<td>91.4% (84.2%–95.4%)</td>
<td>1.03 (0.46-2.29)</td>
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</tbody>
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789PD

Peptide Pharmaceutical Co., Ltd. All other authors have declared no conflicts of interest.

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Safety and immunogenicity of a DNA-vaccine immunotherapy in men with biochemically recurrent prostate cancer


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Background: DNA vaccines INO-5150 (PSA and PSMA) +/- INO-9012 (IL-12) were administered to biochemically recurrent prostate cancer patients (pts) to demonstrate breaking tolerance, assessing antigen-specific humoral and cellular immune responses with the potential for stabilization of disease progression.

Methods: Phase I, open-label, multi-center study in pts post-definitive therapy with a rising PSA after surgery and/or RT and PSA doubling time (DT) > 3 months (mos), testosterone > 150 ng/dL, no concomitant ADT and no evidence of metastases. Safety, immunogenicity and efficacy were evaluated in 4 treatment arms in 60 planned pts (A: 16, 2mg INO-5150; B: 15, 8.5mg INO-5150 + 1mg INO-9012; C: 15, 2mg INO-5150 + 1mg INO-9012; D: 16, 8.5mg INO-5150 + 1mg INO-9012) treated with 4 IM doses followed by electroporation on day 0, wks 3, 12 and 24 who were followed for a total of 72 Wks.

Results: Median age, Gleason score and time since diagnosis were 69.3 yrs (range: 55.4–87.7), 7 (3–10) and 8.4 yrs (0.4–23.8) respectively. Of 61 evaluable pts, 38 (62%) had PSA DT > 12 mos and 23 (38%) had DT ≤ 12 mos, Day 0 and week 27 median DT were 6.0 (1.5, 11.6) mos and 8.1 (2.2, 100) mos respectively. Flow cytometry analysis revealed antigen specific upregulation of CD38 and Perforin on CD8+ T cells in 19/50 (38%) pts across the trial, with the greatest proportion in arm A, 8/14 (57%). Additional analysis for this cell subset showed a high PD-1 expression of 68.6% in this arm at week 27. Of note, in 8/15 (53%) arm A pts with DT ≤ 12 mos, their median DT at Day 0 was 6.2 (2.9, 10.2) mos and 19.2 (6.6, 100) mos at Wk 27. Safety: 7 Grade (Gr) 3 SAIs in 5 pts and 4 Gr 4–5 SAIs reported. Most AIs were Gr 1-3 in 51/62 (82%) pts and majority of those were associated with injection site reactions.

Conclusions: INO-5150 +/- INO-9012 was safe at dosages examined. Data demonstrated both PSA and PSMA are immunogenic and INO-5150 induced cellular immune responses. Higher proportion of arm A pts showed immunological responses as well as improvements in PSA DT, specifically pts with DT ≤ 12 mos suggesting correlation of immunological efficacy and clinical benefit. Continued analyses are planned as patient follow-up is ongoing. (NCT02341213)

Clinical trial identification: NCT02341213; July 29, 2015

Legal entity responsible for the study: Inovio Pharmaceuticals

Funding: Inovio Pharmaceuticals

Disclosure: K. Bhatt: Inovio (study sponsor employee), own stocks M. Morrow, T. McMullan, K. Raynayak, J. Lee, B. Sacchetta, L. Liu, S. Rosencreanz: Inovio (study sponsor employee), own stocks in company. Y. Whang: Research funding from Janssen, Astellas, Tokai, Inovio. I. Csiki, M. Bagarazzi: Employed by Inovio Pharmaceuticals. All other authors have declared no conflicts of interest.
Methods: We performed an immunophenotyping of Pten null prostate murine models by flow cytometry and gene expression analysis. Immunohistochemistry and immunofluorescence stainings were utilized to detect macrophages infiltration in the tumor and marker of proliferation and senescence in the tissue.

Results: We have found that aggressive prostate tumors are strongly infiltrated by TAMs that express alternatively activated M2 markers. Unexpectedly chemokines binding to the C-C-X chemokine receptor type 2 (CCR2) were among the most upregulated factors by TAMs from all tumors and controlled the functional polarization of TAMs toward an “M2-like” functional status. Pharmacological blockade of the CCR2 receptor in different tumor models in vivo promoted the re-education of TAMs toward a pro-inflammatory phenotype, which resulted in induction of senescence and tumor inhibition. Strikingly, infiltrations of CCR2 knockout monocytes in Pten+/−, CCR2−/− mice demonstrated that inhibition of CCR2 does not interfere with the tumor recruitment of monocytes but prevented the polarization of TAMs in M2-like resulting in an increased percentage of TNFα-releasing M1-like macrophages in the tumor microenvironment. Moreover, tumor cells harboring PTEN deletion were more sensitive to TNFα-induced senescence when compared to Pten WT tumors due to increased levels of TNFR1.

Conclusions: Taken together our results identify TAMs as a target for prostate cancer therapy and describe new therapeutic strategies to harness the anti-tumorigenic potential of macrophages in cancer.

Legal entity responsible for the study: Institute of Oncology Research

Funding: ERC/NeiHe

Disclosure: All authors have declared no conflicts of interest.

792PD

Phase I, open-label, dose-finding study of GSK2636771, a phosphoinositide-3 kinase (PI3K)δ inhibitor, in combination with enzalutamide in male subjects with metastatic castration-resistant prostate cancer (mCRPC)

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Background: GSK2636771 is a potent, adenosine triphosphate (ATP) competitive, selective, oral inhibitor of the PI3Kδ isoform that inhibits the growth of phosphatase and tensin homolog (PTEN) deficient tumors in preclinical models. Resistance to the androgen receptor (AR) inhibitor enzalutamide (Xtandi) in PTEN null tumors and controlled the functional polarization of TAMs toward an “M2-like” functional status. Pharmacological blockade of the CCR2 receptor in different tumor models in vivo promoted the re-education of TAMs toward a pro-inflammatory phenotype, which resulted in induction of senescence and tumor inhibition. Strikingly, infiltrations of CCR2 knockout monocytes in Pten+/−, CCR2−/− mice demonstrated that inhibition of CCR2 does not interfere with the tumor recruitment of monocytes but prevented the polarization of TAMs in M2-like resulting in an increased percentage of TNFα-releasing M1-like macrophages in the tumor microenvironment. Moreover, tumor cells harboring PTEN deletion were more sensitive to TNFα-induced senescence when compared to Pten WT tumors due to increased levels of TNFR1.

Conclusions: Taken together our results identify TAMs as a target for prostate cancer therapy and describe new therapeutic strategies to harness the anti-tumorigenic potential of macrophages in cancer.

Legal entity responsible for the study: Institute of Oncology Research

Funding: ERC/NeiHe

Disclosure: All authors have declared no conflicts of interest.

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Phase 1 study of the PSMA-targeted small-molecule drug conjugate EC1169 in patients with metastatic castrate-resistant prostate cancer (mCRPC)

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Background: Prostate-specific membrane antigen (PSMA) is highly expressed in prostate cancers, but not in most non-prostate normal tissues, making it a potential therapeutic target. EC1169 is a PSMA-targeted conjugate of the microtubule inhibitor tubulysin B hydrazide is being studied in a two-part phase 1 dose escalation (A) expansion (B) study in mCRPC. The utility of the PSMA-targeted companion imaging agent 99mTc-EC0652 is also being evaluated as a patient selection tool. Part A has been completed. We now report the part B data on pts treated to date.

Methods: EC1169 is administered as an IV bolus on days 1, 8 every 21 days. The RP2 dose of EC1169 is 6.5 mg/m2 (D1, 8 every 21 days). EC1169 has been studied as a single agent in a Phase 1 study. There is evidence of anti-tumor activity in both the taxane naïve and taxane exposed. Median age is 70 (range: 49-84). Median number of cycles is 3 (range: 1-6). Six of twelve pts have had 6 months. DE of 300 mg and DX of 200 mg cohorts have been completed. We now report the part B data on pts treated to date.

Methods: EC1169 is administered as an IV bolus on days 1, 8 every 21 days. The RP2 dose of 5 mg/m2 was determined in Part A. Part B pts are treated at the RP2 dose and enrolled in 1 of 2 cohorts: mCRPC: taxane naïve (cohort 1, 45 pts) or taxane exposed (cohort 2, 40 pts). Prior to treatment, pts undergo a 99mTc-EC0652 SPECT/CT scan. The primary endpoint of Part B is median radiographic progression-free survival (mPFS). Other study evaluations are OS, PSA, and CTCAE-based biomarkers.

Results: Thirty-four of a planned 85 pts in Part B have been treated (14 taxane naïve, 20 taxane exposed). Median age is 70 (range: 49-84). Median number of cycles is 3 (range: 1-7). Twenty-six pts (76.5%) reported at least 1 treatment related AE. Most treatment related AEs (TRAEs) were Gr1 and 2; TRAE-related constipation occurred in 1 pt. No Grade 4 TRAEs have been reported. No dose reductions due to AEs have occurred. Six of twelve evaluable taxane-exposed pts in Part B had stable disease or better at their first post-baseline scan (9 vsk). One pt currently beyond the 18-week scan has achieved durable resolution of his soft tissue disease. Imaging with 99mTc-EC0652 suggests excellent disease localisation.

Conclusions: The RP2 dose of EC1169 is 6.5 mg/m2 (D1, 8 every 21 days). EC1169 has been well tolerated in 34 Part B pts at the RP2 dose A PSMA-targeted therapeutic strategy appears viable. There is evidence of anti-tumor activity in both the taxane naïve and taxane exposed pts.

Clinical trial identification: NCT02202447

Legal entity responsible for the study: Endocyte, Inc.

Funding: Endocyte, Inc.

Disclosure: A. Armour, M. Groaning: Employee of Endocyte, owns company stock. R. Messmann: Contractor for Endocyte, owns company stock. All other authors have declared no conflicts of interest.
EPI-506 (ralaniten acetate), a novel androgen receptor (AR) N-terminal domain (NTD) inhibitor, in men with metastatic castration-resistant prostate cancer (mCRPC): Phase I update on safety, tolerability, pharmacokinetics and efficacy

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Background: EPI-506 (ralaniten acetate) is being studied in a Phase I/2 study as a first-in-class transcription inhibitor of the AR NTD.

Methods: Open-label, single-arm, Phase I/2 study evaluating EPI-506 administered orally. The Phase I is a modified 3+3 design to establish safety, tolerability, pharmacokinetics (PK), maximum-tolerated-dose (MTD) and the recommended phase 2 dose (RP2D) of EPI-506. Anti-tumor activity is evaluated by PSA and imaging. Inclusion criteria include: mCRPC with progression after ≥1 line of hormonal therapy or chemotherapy, failure to treat with enzalutamide and/or abiraterone.

Results: Twenty-one patients (pts) have been enrolled in the dose escalation phase over 6 dose levels (80–2,400 mg). Median age was 72 (range 58–87). Prior treatments included enzalutamide only (N=9), abiraterone only (N=3) or both (N=9). Eight pts also had prior chemotherapy. Twelve pts discontinued due to disease progression and 2 pts due to adverse events (AEs): Grade 4 elevated amylase (probably related; at 640 mg) and Grade 4 gastrointestinal bleeding (unrelated). Median exposure was 87 days at cut-off (range 21–418). Most frequently reported treatment emergent AEs were diarrhea (N=9), nausea (N=6), and pain in extremities (N=5). One possibly related Grade 3 AE (AST elevation) was observed at 1280 mg. PK data demonstrate a dose-proportional profile for EPI-506 and AUC together with a positive food effect above 640 mg. Three of 21 evaluable pts demonstrated PSA declines ranging from 4–29%, and one pt with unchanged PSA at doses ≥1,280 mg. Three pts have had prolonged exposure regardless to dose levels. One patient had a long administration period exceeded to 15 months without disease progression, and another 1 patient experienced remarkable pain relief induced by bone metastases. toxicity was acceptable and manageable in CRPC pts, and preliminary anti-tumor activity, especially against bone metastases was recognized. A phase II trial for CRPC pts with bone metastases is ongoing.

Clinical trial identification: NCT02606123

Legal entity responsible for the study: ESSA Pharmaceuticals Corp.


SM88 is a non-toxic novel combination therapy based on the Warburg effect, with activity in a variety of cancers including prostate (JCO 2017e Abstract1). Phase I results demonstrated stable or rising testosterone levels while achieving CTC (circulating tumor cells) benefit and no radiographic progression events (JCO 2017e Abstract2). We now report Phase II data.

Results: 174 pts were treated on SM88, including 76 on SM88 monotherapy and 98 with combination therapy. Among the combination pts 104 were on SM88 + abiraterone, 60 on SM88 + enzalutamide, and 1 on SM88 + enzalutamide + docetaxel. Median time on study was 131 days (range 1–297). 9 of 21 evaluable pts demonstrated PSA declines ranging from 30% to 98% (median 31%); 16 pts had stable disease or rising PSA; 24 pts had radiographic progression. When compared to historical controls (Menarini) from the same institute, the median time to first progression (TTP) on SM88 monotherapy was 6.5 months; the median TTP on combination therapy was 5.4 months (P=0.044). 1 pt had a minor clinical response (mCR) on SM88 monotherapy; 1 pt had a PSA progression free survival of 9 months on SM88 monotherapy. 75% of combination pts had TTP ≥3 months compared to 50% in historical controls.

Conclusion: SM88 is a non-metastatic biochemical recurrent prostate cancer phase II trial of SM88 in non-metastatic biochemical recurrent prostate cancer.

Declaration of INTERESTS: G. Diet Pröhl: 1) WT-chen, 2) Dong, 3) Hoffman, 4) Sokaif
1) Tyime Inc, New York, NY, USA, 2) School of Medicine, Stony Brook University, Stony Brook, NY, 3) Tyime Inc, New York, NY, USA, 4) Tyime Inc, Unifomed Services: University of the Health Sciences, Bethesda, MD, USA

Background: Despite toxicity and no clear clinical benefit, non-metastatic recurrent prostate cancer (nmPC) is typically treated with medical castration in North America. SM88 is a non-toxic novel combination therapy based on the Warburg effect, with activity in a variety of cancers including prostate (JCO 2017 e Abstract1). End of phase 1 results demonstrated stable or rising testosterone levels while achieving CTC (circulating tumor cells) benefit and no radiographic progression events (JCO 2017e Abstract2). We now report phase II data.

Methods: Starting in Sep 2016, a prospective Phase Ib/Ii of SM88 (230mg po bid) enrolled recurrent nmPC with rising PSA (PCWG3 definition) and detectable CTUs, but with no radio graphically identified lesions. Results: 10 of 34 planned subjects have completed at least 1 cycle (median 5, range 1–7). Mean age was 69.7 (62–86); all had prior ADT after curative intent RT (70%) or surgery (30%); no patient is currently on ADT. Mean testosterone level (T) was 581.4 ng/
Conclusions: We propose that hormonal castration is not necessary for nmPC disease control based on a preliminary assessment of both Phase Ib and II data of SM88. CTCs and N:L were improved while maintaining normal T. These early biomarker indicators are consistent with the observed 100% radiographic progression free survival and avoidance of additional toxic therapy. A phase III RCT is planned for confirmation of these results.

Legal entity responsible for the study: Tyme Inc

Funding: Tyme Inc

Disclosure: G. Del Priore, S. Hoffmann, G. Sokol: Current or potential ownership of stock or options and/or salary support from Tyme Inc. W-T. Chen, H. Dong: Employee of Vitaxen. Tyme Inc has a commercial relationship with Vitaxen whereby Vitaxen provides blinded results to the CRO supervising the ongoing clinical trial.

Impact of the addition of metformin (Met) to abiraterone (Abi) in metastatic castration-resistant prostate cancer (mCRPC) patients (pts) progressing on Abi treatment: A phase II pilot study

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Background: Abi has become one of the standard 1st line treatments in mCRPC. Cross-talk signalling pathways such as PI3K/Akt/mTOR represent a possible resistance mechanism against Abi. The oral antidiabetic agent Met has been shown to have antiproliferative effects via inhibiting mTOR. We hypothesized that the addition of Met to pts with Abi progression on Abi treatment: A phase II pilot study

Methods: Men with mCRPC experiencing PSA progression on first line Abi were enrolled in this prospective single-arm open-label multicentre Phase II trial. Pts with visceral metastases were excluded. Abi (1000mg qd)/Prednisone (5mg bd) treatment was continued and pts received Met 1000mg bd in addition. Primary endpoint was progression-free survival (PFS) at 12 weeks according to RECIST 1.1 or PCWG2 criteria. Secondary endpoints included PFS, PSA response rate, OS, toxicity and safety. 25 pts were planned to consider the trial uninteresting (H0: PFS at 12 weeks <35%) using a 5% significance level and a 80% power.

Results: 25 pts with a median age of 76 years (IQR 72-82), were included between November 2013-September 2016 in 3 Swiss cancer centres. Median time to development of castration resistance was 19.5 months (IQR 11-24), and median duration on Abi before study entry was 12.1 mts (IQR 8-19). PFS rate at 12 weeks was 12% (3 of 25 pts), median PFS was 9 weeks (IQR 7-11) and median OS 20.7 mts (IQR 14-23). One patient had PSA decline of 30% and another one of 26%, all other had PSA progression. 4 pts (16%) had radiographic progression at week 12. 11 pts (44%) had grade 1 and two pts each grade 2 (8%) or grade 3 (3%) gastrointestinal toxicity (nausea, diarrhea).

Conclusions: The addition of Met to Abi in mCRPC after PSA progression on Abi did not have a substantial impact on PFS or PSA response. Toxicity of Met in combination with Abi was higher than expected.

Clinical trial identification: NCT01677897

Legal entity responsible for the study: Michael Mark

Funding: Janssen

Disclosure: S. Gillessen, R. Cathomas: Advisor for the Janssen on advisory boards. All other authors have declared no conflicts of interest.

Steroid switch: Reversal of resistance to abiraterone acetate (AA) and prednisolone (P) combination in metastatic castration-resistant prostate cancer (mCRPC) patients

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Background: AA+P has shown to improve overall survival (OS) in large, randomized trial in the treatment of mCRPC both in pre and post-docetaxel setting. AA is a steroidal CYP17A1 inhibitor, which suppresses androgen synthesis. Because of secondary mineralocorticoid excess it is licensed in combination with P.

Methods: Based on previous data reporting responses following steroid switch upon progressing during AA+P a prospective study in mCRPC pts was started. (Lorente at al BJC (2014) 111, 2248–2253).

Results: 23 mCRPC pts were treated with AA (1000 mg q.d.) and P (5 mg b.i.d.). Pts characteristics were as follows: median age 73 (95% CI 69-77) years, median Gleason score 8 (7-9), time-span since diagnosis was median 5.6 (3.6-7.8) yrs and all pts had previous docetaxel treatment and received concomitant androgen deprivation treatment. Pts were on AA+P therapy for median 11.4 (6.4-19.8) mos. In case of PSA progression steroid switch has been applied to dexamethasone (D) (0.5 mg q.d). The PSA progression-free survival on AA+D combination was 5 (3.7-5) mos. 13 (57%) pts are still on AA+D treatment. The OS for AA was 53 (39-55) mos.

Table: 799P

<table>
<thead>
<tr>
<th>Schedule</th>
<th>PSA progression-free survival (mos)</th>
<th>PSA (ng/ml) at start</th>
<th>PSA (ng/ml) nadir</th>
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<tr>
<td>AA+P</td>
<td>Median 11.4</td>
<td>99</td>
<td>32.5</td>
</tr>
<tr>
<td>95% CI</td>
<td>6.4–19.8</td>
<td>30-129</td>
<td>13-98</td>
</tr>
<tr>
<td>AA+D</td>
<td>Median 5</td>
<td>52</td>
<td>41.5</td>
</tr>
<tr>
<td>95% CI</td>
<td>3.7–5</td>
<td>27-133</td>
<td>20-100</td>
</tr>
</tbody>
</table>

During AA+P therapy >25% decrease in PSA occurred in 65% of pts and further decrease (>25%, compared to the nadir during AA+P treatment) has been seen in 26% pts during AA+D treatment.

Conclusions: D can induce further response during AA therapy by reversing glucocorticoid receptor activation or by superior activity of D administered even as a single agent. Our data supports that steroid switch may induce further PSA regression.

Legal entity responsible for the study: Fruzsina Gyergyay

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Background: several drugs are approved in prostate cancer (PC), both in localized and metastatic setting. Challenge of daily practice is the sequencing of available agents for optimal disease management. Trying to extract actionable information from the overall history of disease for each patient remains a difficult task but could provide new insights for better sequencing. This retrospective analysis aimed to follow-up patients included in the Rising-PSA phase 3 clinical trial (R-PSA-CP-03) until death or last contact.

Methods: we retrospectively analyzed therapies received by pts included in R-PSA at the HEIG hospital (Paris, France). Drugs were coded in 8 categories: LH: LHRR modulators, AA: anti-androgens, AA2: new generation AA, DC: docetaxel, CZ: cabazitaxel, EX: blinded experimental drugs, P: therapeutic pause, PCB: placebo/experimental.

Conclusions: on our knowledge, this is the first attempt to model the entire course of PC taking into account both therapies and sequence. Given the complexity of our model, these results should be validated with further studies and methods.

Clinical trial identification: R-PSA-CP-03

Legal entity responsible for the study: ARTIC

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Table: 800P

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>AA+D pre-CT (n = 14) N %</th>
<th>AA+D post-CT N %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Median)</td>
<td>72.9 60-85</td>
<td>72.9 66-78</td>
</tr>
<tr>
<td>Baseline PSA</td>
<td>26.6 45-367</td>
<td>39.9 6-1800</td>
</tr>
<tr>
<td>Gleason 6-7</td>
<td>5 36 8 57 1 7</td>
<td>6 50 6 50</td>
</tr>
<tr>
<td>ECOG 0-1</td>
<td>13 80 1 7</td>
<td>12 100</td>
</tr>
<tr>
<td>Metastases</td>
<td>12 86 8 57 1 7</td>
<td>12 100 4 33 3 25</td>
</tr>
</tbody>
</table>

Conclusions: In selected clinically stable mCRPC patients the P to D switch as adjuvant of AA could be an acceptable and active therapeutic option. Biomarkers correlation of AA could be an acceptable and active therapeutic option. Biomarkers correlation of AA could be an acceptable and active therapeutic option. Biomarkers correlation of AA could be an acceptable and active therapeutic option.
## Clinical trial identification

NCT01715285 (LATITUDE), NCT00399885 (CHAARTEDE), NCT01047153 (GETUG-AFU 15)

## Legal entity responsible for the study:

Janssen Global Services, LLC

**Funding:** Janssen Global Services, LLC


A. Abogunrin: Employment: Evidera Research Funding: Janssen, Novartis, GSK, Shire, Sanofi, Amgen, Pfizer, Bayer, Ipsen, Clovis, AstraZeneca, Boehringer Ingelheim. K. Fizi: Honoraria, Consulting/Advisory Role; Astellas, Bayer, Clovis, Carevac, Genentech, Janssen, Oncon, Sanofi. All other authors have declared no conflicts of interest.

## Background:

Radiographic progression-free survival (rPFS) was observed in the LATITUDE trial, with a median rPFS of 0.92 [0.69, 1.23] percent. The trial demonstrated the efficacy of abiraterone acetate in combination with prednisone and ADT (ADT + AA-P) vs ADT in newly diagnosed mHSPC pts with high-risk disease (NDx HRD). We performed an indirect comparison to determine the relative efficacy of AA vs DOC in mHSPC.

### Methods:

We conducted a systematic literature review of randomized controlled trials (RCTs) of treatments for mHSPC. To increase comparability of results across studies, the population of interest from LATITUDE and DOC studies was restricted to men diagnosed between 2006 and 2010, the later cohort was more likely to receive treatment (37% vs 22%). Compared with the cohort diagnosed between 2011 and 2016, the later cohort was more likely to receive treatment

### Results:

The results for HRD/HVD suggested improvement with ADT + AA-P vs DOC + ADT in OS (HR 0.84 and in rPFS (HR 0.73), with Bayesian probabilities (P) for ADT + AA-P of 96.8% (OS) and 99.2% (rPFS) more effective. Main results were consistent with all sensitivity analysis results (Table).

### Conclusions:

Our analyses suggest that ADT + AA-P has greater reduction in risk of progression and death vs ADT + DOC. In absence of head-to-head trials, indirect comparisons based on Bayesian NMA can provide useful insights to clinicians and reimbursement decision makers on the relative efficacy of treatment options for men with mHSPC.

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**803P**

## Indirect comparison of abiraterone acetate and docetaxel for treatment of metastatic “hormone-sensitive” prostate cancer

S. Feyenbertend, F. Saad, T. Liu, T. Ito, J. Diehl, S. Van Sanden, P. De Porre, J. Roiz, A. Abogunrin, K. Fizazi


### Background:

Androgen deprivation therapy (ADT) with or without chemotherapy (docetaxel [DOC]) is recommended in the clinical guidelines as the mainstay of management for metastatic “hormone-sensitive” prostate cancer (mHSPC). The LATITUDE trial demonstrated the efficacy of abiraterone acetate in combination with prednisone and ADT (ADT + AA-P) vs ADT in newly diagnosed mHSPC pts with high-risk disease (NDx HRD). We performed an indirect comparison to determine the relative efficacy of AA vs DOC in mHSPC.

### Methods:

We conducted a systematic literature review of randomized controlled trials (RCTs) of treatments for mHSPC. To increase comparability of results across studies, the population of interest from LATITUDE and DOC studies was restricted to men diagnosed between 2006 and 2010, the later cohort was more likely to receive treatment (37% vs 22%). Compared with the cohort diagnosed between 2011 and 2016, the later cohort was more likely to receive treatment

### Results:

The results for HRD/HVD suggested improvement with ADT + AA-P vs DOC + ADT in OS (HR 0.84 and in rPFS (HR 0.73), with Bayesian probabilities (P) for ADT + AA-P of 96.8% (OS) and 99.2% (rPFS) more effective. Main results were consistent with all sensitivity analysis results (Table).

### Conclusions:

Our analyses suggest that ADT + AA-P has greater reduction in risk of progression and death vs ADT + DOC. In absence of head-to-head trials, indirect comparisons based on Bayesian NMA can provide useful insights to clinicians and reimbursement decision makers on the relative efficacy of treatment options for men with mHSPC.

## Table: 803P

<table>
<thead>
<tr>
<th>ADT + AA-P vs ADT</th>
<th>ADT + DOC vs ADT</th>
<th>ADT + AA-P vs ADT + DOC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LATITUDE</strong></td>
<td><strong>CHAARTEDE</strong></td>
<td><strong>GETUG-AFU 15</strong></td>
</tr>
<tr>
<td>HVD &amp; HRD</td>
<td>HVD</td>
<td>HVD</td>
</tr>
</tbody>
</table>

### Main analysis

| OS | X | X | X | 0.84 [0.63, 1.14] | 86.8% |
| pPFS | X | X | X | 0.73 [0.57, 0.94] | 99.2% |

### Sensitivity analysis

| OS | X | X | X | 0.92 [0.69, 1.23] | 72.2% |
| OS | X | X | X | 0.79 [0.61, 1.03] | 96.0% |
| pPFS | X | X | X | 0.80 [0.63, 1.02] | 96.6% |

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**804P**

## Practice patterns in metastatic castration-resistant prostate cancer (mCRPC): Evidence from the veterans health administration


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### Background:

Practice patterns for metastatic castration-resistant prostate cancer (mCRPC) have evolved over the last decade due to introduction of agents such as abiraterone and enzalutamide. This study examines mCRPC treatment practices over a 10-year period (which includes the time periods before and after the introduction of novel oral anti-androgens) for the first 3 lines of therapy in the largest nationwide integrated health system in the United States, the Veterans Health Administration.

### Methods:

By linking patient information from the Veterans Affairs (VA) Clinical Cancer Registry to clinical notes, laboratory, procedure and imaging data from the VA Corporate Data Warehouse (CDW), we identified patients who were diagnosed with prostate cancer at the VA and ultimately developed mCRPC, defined as radiological evidence of metastasis and evidence of rising PSA levels concomitant with surgical (bilateral orchectomy) or medical castrate testosterone levels (< 50 ng/dL) within the last 3 months or ongoing treatment with androgen deprivation). Therapies used to treat mCRPC were extracted from CDW pharmacy dispensation records (docetaxel, abiraterone, enzalutamide, cabazitaxel, and others).

### Results:

From 2006 to 2015, 128,374 patients were diagnosed with prostate cancer, of whom 3,637 developed mCRPC. Median age at initial prostate diagnosis was 68 years (range, 41-94), average BMI was 26.5 (range, 9-59), average CCI score was 1.5 (range, 0-12) and average PSA was 45.5 ng/mL. Practices for the first 3 lines of treatment from 2006 to 2010 and 2011 to 2016 are summarized in Table 1. Patients diagnosed with mCRPC between 2006 and 2010 were more likely to receive cytotoxic therapy than patients diagnosed between 2011 and 2016 (37% vs 22%). Compared with the cohort diagnosed between 2016 and 2010, the later cohort was more likely to receive treatment

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doi:10.1093/annonc/mdx370 | 177
(44% vs 62%) and was also more likely to receive > 1 line of therapy (29% vs 37%). For patients diagnosed between 2011 and 2016, the most common therapies were as follows: 1L, abiraterone (29%); 2L, abiraterone (15%) and enzalutamide (14%); and 3L, enzalutamide (8%).

Conclusions: Our study is the first to describe adoption of non-chemotherapeutic treatments in a nationwide cohort of patients with mCRPC treated in the largest integrated healthcare system in the United States. Further research will focus on understanding clinical outcomes associated with this shift in practice patterns.

Legal entity responsible for the study: Ahmad Halwani, MD

Funding: Genentech, Inc.


Legal entity responsible for the study: Shanghai Changhai Hospital. 168 Changhai Road, Shanghai 200433, China

Funding: AstraZeneca

Disclosure: All authors have declared no conflicts of interest.

RO6P

Outcomes of prechemotherapy (pCrx) abiraterone acetate (AA) or enzalutamide (E) for metastatic castration-resistant prostate cancer (mCRPC) after ADT + Docetaxel (D) or ADT alone for metastatic hormone sensitive prostate cancer (mHSPC) in a multi-institution hospital-based registry

E. Francis1, S. Yip1, N.S. Ahmed1, H. Li2, L. Ardolino4, C.P. Evans1, M. Kaymakcalan1, G.R. Shaw1, P. Kantoff5, M.E. Taplin1, N. Alimohamed2, A.M. Joshua1, D.Y.C. Heng1, C.J. Sweeley1

1Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; 2Genitourinary Oncology, Tom Baker Cancer Centre, Calgary, AB, Canada; 3Departments Oncology and Community Health Sciences, University of Calgary, Calgary, AB, Canada; 4Medical Oncology, Saint Vincent's Hospital, Sydney, Australia; 5Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Background: The E3805: CHAARTED trial noted that the addition of D to ADT was associated with a hazard ratio (HR) of 0.56 (95% confidence interval [CI], 0.44 to 0.70; P < 0.001) for time to CRPC and resulted in a prolongation of overall survival (OS). Therefore, we postulated that pCrx AA or E had greater activity after ADT+D compared to after ADT alone.

Methods: A cohort of mCRPC patients (pts) treated with pCrx AA or E for mCRPc between 2014 and 2017 was identified from three hospitals’ IRB approved databases. Patients were grouped by use of D for mHSPC. This time frame was chosen as ADT+D became a valid therapeutic option for mHSPC in 2014 and thus time to pCrx and follow-up were short. The endpoints included OS (time to death from all causes) from ADT start, time to AA/E start from ADT start, and OS from AA/E start. Survival outcomes were analyzed by Kaplan-Meier method.

Results: Of the 102 identified, 50 (49%) had previously received ADT alone, while 52 (51%) had ADT+D. No statistically significant difference in OS from ADT start or from AA/E start was observed between the 2 cohorts (Table 1). Notably, survival in both groups from ADT start was shorter than commonly reported. Yet, deaths in the ADT+D group were 12 vs. 21 in the ADT alone, after a median follow-up of 24.4 and 29.8 months, respectively.

Table: 804P

<table>
<thead>
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<tbody>
<tr>
<td>1L, % pts 2L, % pts 3L, % pts</td>
<td>DOC 27%, AA 22%, ENZ 6% AA 13%, ENZ 10%, DOC 4% ENZ 6%, DOC 4%, AA 3%</td>
<td>DOC 37%, AA 4%, ENZ 1% AA 7%, MIT 5%, CAB 3% AA 3%, ENZ 2%, DOC 2%</td>
</tr>
<tr>
<td>No treatment, % pts</td>
<td>1L 43%, 2L 68%, 3L 80%</td>
<td>1L 56%, 2L 80%, 3L 90%</td>
</tr>
<tr>
<td>Top 3 most common treatment sequences from 1L to 2L (of pts)</td>
<td>DOC-AA (11%) AA-ENZ (8%) AA-DOC (4%)</td>
<td>DOC-AA (7%) DOC-MIT (5%) DOC-CAB (3%)</td>
</tr>
</tbody>
</table>

AA, abiraterone acetate; CAB, cabazitaxel; DOC, docetaxel; ENZ, enzalutamide; MIT, mitoxantrone. *<15 patients were treated with radium-223 dichloride or sipuleucel-T.
Conclusions: In a cohort of ADT/ADT+D treated mCRPC pts with short times to pCRx AA/E and follow-up, the efficacy of AA/E is similar regardless of previous use of D. It is possible that the pts selected for ADT+D had poorer prognostic factors and yet still did at least as well with AA/E and deaths were lesser. Larger sample sizes, longer follow-up, and better characterization of patient and tumor factors are needed to assess the efficacy of different sequences.

Legal entity responsible for the study: Edoardo Francini

Funding: None


<table>
<thead>
<tr>
<th>Table: 807P Baseline characteristics and treatment completion by prior or concomitant* abiraterone/ enzalutamide (abir/Enza)</th>
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<tr>
<td>Prior Yes (n = 168)</td>
</tr>
<tr>
<td>ECOG 0–1, n (%)</td>
</tr>
<tr>
<td>No. of metastases**, n (%)</td>
</tr>
<tr>
<td>&lt;5</td>
</tr>
<tr>
<td>6–20</td>
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<tr>
<td>&gt;20</td>
</tr>
<tr>
<td>Superscan</td>
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<tr>
<td>ALP (U/L), median</td>
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<tr>
<td>&lt;140 U/L, n (%)</td>
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<td>&gt;140 U/L, n (%)</td>
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<tr>
<td>PSA (ng/mL), median</td>
</tr>
<tr>
<td>LDH (U/L)***, median</td>
</tr>
<tr>
<td>Prior docetaxel or cabazitaxel, n (%)</td>
</tr>
<tr>
<td>Completed 5 or 6 Ra-223 doses, n (%)</td>
</tr>
</tbody>
</table>

*Prior = abir/Enza stopped before starting Ra-223. Concomitant = any overlap with Ra-223.

**Pts undergoing more than one imaging modality may be reported in multiple categories.

***LDH was available for 209/583 patients.

Background: Ra-223 prolongs survival with a favorable safety profile in metastatic castration-resistant prostate cancer (mCRPC). The pivotal phase 3 ALSYMPCA trial had a relatively short 3-year follow-up and was conducted before availability of 2nd generation hormonal agents. The REASSURE study was designed to assess long-term safety (7 years follow-up) and conducted in an era when pts had access to other effective 1st line agents such as abir/enza.

Methods: REASSURE is a global, prospective, single-arm, observational study that enrolled pts with mCRPC with bone metastases planned to start Ra-223. Treatment decision was made independently before enrollment. We undertook a planned interim descriptive analysis of safety and drug completion based on prior or concomitant abir/enza use.

Results: REASSURE enrolled 1106 pts in N. America and Europe from Sep 2014 to Sep 2016. The interim analysis included 583 pts who received >1 Ra-223 dose (Table; median 7 months observation). Prior abir/enza use was reported in 168 (29%) and concomitant in 153 (26%) pts. Treatment-related adverse events (TRAEs) occurred in 37%: prior abir/enza 45%, no prior abir/enza 34%; concomitant abir/enza 29%, no concomitant abir/enza 40%. TRAEs were most often gastrointestinal or hematological, with permanent discontinuation of Ra-223 in 6%: prior abir/enza 8%, no prior abir/enza 9%; concomitant abir/enza 9%, no concomitant abir/enza 7%. Serious TRAEs (mostly hematologic) occurred in 4.5% leading to permanent Ra-223 discontinuation in 1.5%.
Background: Older men are at risk for adverse events (AEs) from androgen deprivation therapy (ADT). In prior studies, peripheral androgen blockade with bicalutamide and finasteride (Fin) in men ≥65 years with hormone-naive systemic prostate cancer (HNPCa) was better tolerated but less efficacious than ADT in HNPCa. The potential synergy of Enz with Dut/Fin appears to be safe and efficacious for older patients with prostate cancer.

Methods: Phase IV, non-randomized, open-label, single-arm interventional study, with men aged ≥65 years (or <65 years and 25% irradiated bone marrow), presenting mCRPC after docetaxel failure, ECOG status ≤1, life expectancy >12 weeks, who provided informed consent. Cabazitaxel 25 mg/m² was given with prednisone one day every 21 days. G-CSF was administered on days 2 to 8 of each cycle or until ANC >2,000/mm³ and ciprofloxacin 1000mg on days 3 to 5. Primary endpoint was the rate of neutropenia grade ≥3 during the first cycle; secondary endpoints were the rate of neutropenia grade ≥5, febrile neutropenia ≥5, PSA response and quality of life (FACT-P) during treatment. Statistical significance was set at 0.05 and 95% confidence intervals were determined.

Results: 46 patients with median age 71.5 years (mean: 71.8 years) and 68.9 months on median since diagnosis (median: 75.2 months) of prostate cancer were included. Among the 45 treated patients, exposed to a median of 9.0 cycles (mean: 9.5 cycles) during 210 days, 40.0% (95% CI, 25.7%-54.3%) presented one episode of neutropenia grade ≥3 during the first cycle. During treatment, 42.2% patients presented at least one neutropenia grade ≥3; febrile neutropenia occurred in one patient (2.2%) as well as diarrhea grade ≥3. Twenty-nine patients (64.4%) achieved PSA response and 77.2% improved FACT-P score in at least one visit. Three patients (6.7%) had a serious TEAEs leading to death (none related to treatment), and 13.3% had 7 TEAEs leading to treatment discontinuation (3 related to treatment).

Conclusions: Prophylactic G-CSF and ciprofloxacin was effective in the prevention of neutropenia grade ≥3 and other hematological complications during this treatment with cabazitaxel 25 mg/m² in patients who were at risk for neutropenia.


Legal entity responsible for the study: Sanofi

Funding: Sanofi


Assessment of health-related quality of life (HRQL) in PROSELICA: A Phase 3 trial assessing cabazitaxel 20 mg/m² (C20) or 25 mg/m² (C25) in post-docetaxel (D) patients (pts) with metastatic castration-resistant prostate cancer (mCRPC)
cycles, change in FACT-P TS from BL to Cycle 10 favored C25 but not C20 (C25 n = 140: 3.06 [95% CI 0.25, 5.86], p = 0.033; C20 n = 137: 2.67 [95% CI -0.17, 5.51], p = 0.063). Difference in change was not significant for C20 vs C25 (0.39 [95% CI -0.66, 2.88], p = 0.816). For evaluable pts who received ≤ 6 cycles, change in FACT-P TS from BL to Cycle 6 favored pts receiving C25 (C25 n = 49: 4.61 [95% CI -8.27, 9.5], p = 0.014; C20 n = 39: -6.58 [95% CI -10.46, -2.69], p = 0.001) but the difference between the treatment arms was not significant (-1.96 [95% CI -6.8, 2.97], p = 0.426). Increasing cycles, BL ECOG performance score (0-1 vs ≥ 2) and receiving >6 cycles significantly improved FACT-P TS change from BL (p = 0.001). Difference in treatment dose (C20 vs C25) did not have a significant effect on FACT-P TS change from BL (p = 0.334).

Conclusions: In the overall population, HRQL did not differ significantly from BL to Cycle 10 for C20 vs C25. Additionally, there were no significant differences between the two treatment arms (C20 vs C25) in either subgroup (> 6 or ≤ 6 cycles). A significant change in HRQL from BL to Cycle 10 was observed in patients who received >6 cycles of C25. Funding: Sanofi.

Clinical trial identification: NCT01308580

Legal entity responsible for the study: Sanofi

Funding: Sanofi

Disclosure: D. Ford: Honoraria from Astellas and Sanofi. L. Mourey: Personal fees and non-financial support from Sanofi, Astellas, Pfizer and Novartis, personal fees from Ipsen and Sandoz, non-financial support from Roche, grant from GSK. J. Carles: Consultancy role for Johnson & Johnson, Bayer, Astellas, BMS, Pfizer and Sanofi. G. Kació: Advisory boards and/or conferences for Amgen, Astellas, AstraZeneca, Bayer, Ipsen-Beaufour, Jansen, Novartis, Pfizer and Sanofi, clinical trials for Astellas, Ipsen-Beaufour, Jansen, Novartis and Sanofi. G. Barnes: Consultant for Sanofi. H. Wang: Employee of Sanofi and own Sanofi stock. Previously employed by Merck & Co. W. Zhang: Consultant for Sanofi. A. Ozatilgan: Employee of Sanofi. J. de Bono: Grants and personal fees from Sanofi, AstraZeneca, Genentech and Genmab, personal fees from Pfizer, Merck Serono, Daichi-Sankyo, grant from Taiho. All other authors have declared no conflicts of interest.

CABAZITAXEL FOLLOWED BY ANDROGEN DEPRIVATION THERAPY (ADT) SIGNIFICANTLY IMPROVES TIME TO PROGRESSION IN PATIENTS WITH NEWLY DIAGNOSED METASTATIC HORMONE SENSITIVE PROSTATE CANCER (mHSPC): A RANDOMIZED PHASE 3 STUDY (FACT-PV) A. Antinari,1 A. Widmark,1 A. Falt,1 E. Uvskog,1 S. Davidson,1 C. Thellenberg Karlsson,1 M. Tjernström1 1Department of Urology, Faculty of Medicine and Health, Orebro University, Orebro, Sweden.2Department of Radiation Sciences, Oncology, Umeå University, Umeå, Sweden.3Department of Epidemiology and Biostatistics, Faculty of Medicine and Health, Orebro University, Orebro, Sweden.4Department of Oncology, Uppsala University, Uppsala, Sweden.5Department of Oncology, Karolinska Institutet, Stockholm, Sweden

Background: Patients with newly diagnosed mHSPC have a poor prognosis with a 3-year overall survival (OS) rate of 50%. Recently, combination of docetaxel (75mg/m2 every 6 weeks for 6 cycles) with ADT has become a new standard for such patients, based on results of 2 large phase 3 trials showing a significant OS benefit. In these trials, docetaxel was initiated within 6 months after ADT start. Timing of ADT and chemotherapy (CT) is controversial. In breast cancer, endocrine therapy is always started after CT, the rationale being that ADT within 3 months after ADT start. Timing of ADT and chemotherapy (CT) is controversial. Observational studies are in progress to gather real-world treatment patterns, safety, efficacy and HRQL effect of CRPC treatment beyond clinical trials.

Methods: The prospective, observational study CAPRISTANA evaluated the routine clinical use of CBZ (25 mg/m2 every 3 weeks plus prednisone 10 mg/day) in pts with mCRPC previously treated with docetaxel. HRQL was assessed using Functional Assessment of Cancer Therapy - Prostate (FACT-P) version 4 and EQ-5D-3L (including VAS - visual analogue scale) questionnaires at baseline and every two cycles until CBZ discontinuation.

Results: A total of 192 pts were treated in 55 centers across 6 countries (April 2012–June 2016); 161 and 157 pts were evaluable for FACT-P and EQ-5D-3L, respectively. Pts received 6 (median) cycles of CBZ (range 1–24); 53.6% achieved disease control with CBZ. The main reason for CBZ treatment discontinuation was disease progression (58.3%). No new safety signals were identified. In the overall FACT-P score analysis, HRQL improvement during CBZ treatment was recorded in 31.8%, no change in HRQL in 40.4%, and deterioration was recorded in 27.8% of pts. The highest rate of improvement was observed for the Prostate-Specific Concerns subscale (49.3%) and Pain Control subscale (52.4%). The highest rate of deterioration was for the Functional Well-Being subscale (42.0%). Mean FACT-P score and EQ-5D-3L health utility index and VAS scores did not show statistically significant changes during CBZ treatment.

Conclusions: In this real-world study investigating HRQL associated with the use of CBZ in pts with mCRPC, no significant changes were observed in mean on-treatment FACT-P score and EQ-5D-3L scores. However, in contrast to observations in prospective clinical studies, pts had improvement in the Pain Control FACT-P subscale. These results suggest that, in addition to the previously demonstrated effectiveness, CBZ treatment may help pts to achieve better pain control.

Legal entity responsible for the study: Sanofi

Funding: Sanofi

Disclosure: G. Barnes: Employee of Sanofi M. Ghosn: Advisory boards for Sanofi, Astellas and Jansen. I. Koroileva: Research funding and speakers’ bureau for AstraZeneca and Teva, travel reimbursement from MSD and Eisai. A. Ozatilgan: Employee of Sanofi. S. Hitter: Employee of Sanofi. J. Carles: Consulting/advisory role to Johnson & Johnson, Bayer, Astellas, BMS, Pfizer and Sanofi. All other authors have declared no conflicts of interest.

Real-world use of docetaxel for metastatic castration-resistant prostate cancer (mCRPC) in China: Results from a large observational study

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Background: This study investigated real-world patterns of docetaxel use for metastatic castration-resistant prostate cancer (mCRPC) in China.
Methods: A prospective, multi-centre, observational study of Chinese adults (≥18 years) with histologically confirmed metastatic prostate adenocarcinoma who received ≥1 dose of docetaxel following hormonal therapy failure (disease progression and serum testosterone <50 ng/dL). The primary endpoint was patterns of docetaxel use. Secondary endpoints included median overall survival (mOS), prostate-specific antigen (PSA) response rate (RR) and reasons for docetaxel discontinuation. Variables are summarised as mean (SD) unless specified. All patients provided written informed consent.

Results: From August 2011 to June 2016, 403 patients were enrolled at 32 centres and 315 (78.2%) completed the study. The mean number of docetaxel cycles and dose were 4.4 (2.86) and 46.9 mg/m2 (9.12), and treatment compliance was 94.0% (10.94%). mOS was similar for docetaxel after 1st- or 2nd-line hormonal therapy (Table), and was longer in patients without visceral metastases versus those with visceral metastases (23.3 months vs. 17.4 months, P = 0.019). Planned docetaxel treatment was completed by 30.8% (124) of patients; the most common reasons for discontinuation were ‘other reasons’ (23.9% [94]), cost of medical expenses (22.6% [91]), and tumor progression (14.1% [57]). Treatment-emergent AEs (TEAs) occurred in 28.8% (64), and serious TEAs in 4% (16), of patients.

Conclusions: Around three-quarters of Chinese mCRPC patients treated with docetaxel initiate treatment after failure of 1st- or 2nd-line hormonal therapy and mOS and PSA RR are similar in both settings. Docetaxel was relatively well tolerated.

Legal entity responsible for the study: Sanofi-Aventis

Funding: Sanofi-Aventis

Disclosure: All authors have declared no conflicts of interest.

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Table: B13P

<table>
<thead>
<tr>
<th>Pattern of use of docetaxel in Chinese patients with mCRPC</th>
<th>n (%)</th>
<th>Median overall survival, months (95% CI)</th>
<th>PSA response rate, % (n/n*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>403 (100)</td>
<td>22.4 (20.4, 25.8)</td>
<td>70.9 (168/237)</td>
</tr>
<tr>
<td>After failure of 1st-line hormonal therapy</td>
<td>170 (42.2)</td>
<td>22.5 (19.2, 29.5)*</td>
<td>73.6 (64/87)</td>
</tr>
<tr>
<td>After failure of 2nd-line hormonal therapy</td>
<td>125 (31.0)</td>
<td>23.3 (18.1, 26.5)*</td>
<td>67.1 (55/82)</td>
</tr>
<tr>
<td>After failure of ≥ 3rd-line hormonal therapy</td>
<td>51 (12.7)</td>
<td>22.4 (19.0, 36.5)</td>
<td>65.4 (17/26)</td>
</tr>
<tr>
<td>After failure of estramustine therapy</td>
<td>46 (11.4)</td>
<td>20.2 (16.6, 27.7)</td>
<td>69.7 (23/33)</td>
</tr>
<tr>
<td>Other</td>
<td>11 (2.7)</td>
<td>28.6 (17.5, not evaluable)</td>
<td>100.0 (9/9)</td>
</tr>
</tbody>
</table>

*Denominator is the number of patients in each category who had PSA ≥20 ng/mL at baseline;
*p = 0.781 for median overall survival with initiation of docetaxel following failure of 1st- and 2nd-line hormonal therapy.

mHSPC, metastatic hormone-sensitive prostate cancer; PSA, prostate specific antigen.

---

B14P

Longer time from diagnosis to docetaxel treatment results in a shorter survival in metastatic hormonosensitive prostate cancer (mHSPC) patients treated with chemotherapy+androgen deprivation therapy (ADT)

M.A. Climent Durán1, B. Mellado2, J.M. Piulats Rodriguez3, M.J. Juan1, M.I. Sáez1, D. Berg1, A. Montesana1, F. de Braud1, R. Montone3, F. Pantano3, G. Procopio1, D. Santini2, G. Verzoni1, R. Ratta1, E. Verzoni1, R. Montone3, F. de Braud1, D. Santini2, G. Procopio1

1Medical Oncology, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, 2Medical Oncology, Hospital Clinic, Barcelona, Spain, 3Medical Oncology, Hospital San Juan Despi, Badalona, Spain

Background: Several solid tumors. The aim of this study was to examine the prognostic role of baseline neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR) and NLR, PLR and LMR changes at 1, 2 and 3 months in patients with metastatic castration-resistant prostate cancer (mCRPC) treated with abiraterone acetate (AA) in pre-docetaxel setting.

Methods: We retrospectively included mCRPC pts treated with AA at 2 Italian hospitals from November 2012 to April 2017. NLR, PLR and LMR were evaluated at baseline and after 1, 2 and 3 months of treatment. The impact of NLR, PLR and LMR on progression-free survival (PFS) was evaluated by Cox regression analyses both in univariate and multivariate fashion. Other clinico-pathological factors, such as PSA baseline level, Time to CRPC, Gleason Score, Presence of Visceral Metastases and Bone Metastases Burden were included.

Results: Fifty mCRPC pts treated with AA were evaluated. At univariate analysis, elevated baseline NLR and PLR were significantly associated with shorter median PFS (p = 0.01, hazard ratio [HR] = 1.224 and p = 0.0001, HR = 1.013 respectively); after 1

Annals of Oncology
month of treatment, NLR and PLR were significantly predictors of worst PFS (p = 0.03, HR = 1.320 and p = 0.02, HR = 1.102 respectively). After 2 and 3 months of treatment, only high NLR was associated with poor prognosis (p = 0.01, HR = 1.012 at month 2; p = 0.009, HR = 1.009 at month 3 respectively). LMR didn't show any prognostic relevance. At multivariate analysis, only baseline PLR was independently associated with PFS (p = 0.006, HR = 1.013).

Conclusions: High baseline and early-assessed NLR and PLR during treatment with AA are associated with worse PSADT. PSMA-PET/CT more than PSA should be considered as an early and easy-to-perform prognostic marker in this setting.

Legal entity responsible for the study: Instituto Coimbra, Portugal

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Table: 817P Distribution and 3-year cancer-specific survival rates for different scores in the evaluated cohort

<table>
<thead>
<tr>
<th>Score</th>
<th>N(%)</th>
<th>3-year cancer-specific survival rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1024 (11.7%)</td>
<td>98%</td>
</tr>
<tr>
<td>1</td>
<td>1639 (18.8%)</td>
<td>97%</td>
</tr>
<tr>
<td>2</td>
<td>898 (10.3%)</td>
<td>91%</td>
</tr>
<tr>
<td>3</td>
<td>2161 (24.8%)</td>
<td>88%</td>
</tr>
<tr>
<td>4</td>
<td>2537 (29.1%)</td>
<td>79%</td>
</tr>
<tr>
<td>5</td>
<td>466 (5.4%)</td>
<td>76%</td>
</tr>
</tbody>
</table>

Conclusions: Prostascore is an easy and reliable tool for predicting the outcomes of patients with treatment-naïve advanced prostate cancer. Further validation within the context of other treatment settings and population-based cohorts is recommended.

Legal entity responsible for the study: Omar Abdel-Rahman

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Background: We previously reported a relationship between PSADT and MFS in men with biochemically recurrent prostate cancer (BRPC) after radical prostatectomy (RP): Implications for patient counseling and clinical trial design

M. Markopoulos $^{1}$, Y. Chen $^{2}$, Z. Feng $^{2}$, B. Trock $^{3}$, J. Cullen $^{4}$, D. Suzman $^{1}$, E. Antonarakis $^{1}$, L. Taler $^{1}$, M. Han $^{1}$, A. Patan $^{1}$, M. Eisenberger $^{1}$

$^{1}$Oncology, Johns Hopkins University, Baltimore, MD, USA; $^{2}$Surgery, Center for Prostate Disease Research, Rockville, MD, USA; $^{3}$Urology, Johns Hopkins University, Baltimore, MD, USA; $^{4}$Surgery, Center for Prostate Disease Center, Rockville, MD, USA; $^{5}$Department of Medical Oncology, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD, USA; $^{6}$Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, Baltimore, MD, USA

Background: We performed a retrospective analysis in 29 localized prostate cancer patients of three private Brazilian cancer institutions who underwent PSMA-PET/CT for rising PSA after treatment with curative intent. The clinical impact of PSMA-PET/CT was evaluated by whether the assistant physician changed or not the treatment strategy based solely on PSMA results. In addition, modifications related to local (surgery, chemotherapy) or systemic (antiandrogen deprivation therapy [ADT], chemotherapy [chemo]) treatment were described.

Results: In total, 29 patients were enrolled. Twenty-seven (93%) had undergone radical prostatectomy, and 2 (7%) radiotherapy as the local curative treatment. Sixteen cases (55%) had not received any radiotherapy previously. The mean Gleason score, PSA level and PSADT at time of the examination were 8, 4.2 (0.05-41) ng/ml and 4.4 (0.4-2537) months, respectively. PSMA-PET/CT detected at least one suspicious lesion for loco-regional and distant disease in prostate cancer patients with biochemical relapse. Even with low levels of PSA, PSMA imaging is able to identify metastatic lesions, being a possible tool for tailoring treatment decisions. This study aims to describe the use of PSMA-PET/CT in the daily practice and its clinical impact in the management of prostate cancer patients who have rising PSA after curative treatment.

Methods: We performed a retrospective analysis in 29 localized prostate cancer patients of three private Brazilian cancer institutions who underwent PSMA-PET/CT for rising PSA after treatment with curative intent. The clinical impact of PSMA-PET/CT was evaluated by whether the assistant physician changed or not the treatment strategy based solely on PSMA results. In addition, modifications related to local (surgery, chemotherapy) or systemic (antiandrogen deprivation therapy [ADT], chemotherapy [chemo]) treatment were described.

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Table: 818P

<table>
<thead>
<tr>
<th>PSAADT</th>
<th>Median metastasis-free survival (year)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Proximal PSA&lt;10 ng/mL</td>
</tr>
<tr>
<td>6.01-12 mths</td>
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<td>7 (n = 106)</td>
</tr>
<tr>
<td>&lt; = 3 mths</td>
<td>3 (n = 48)</td>
</tr>
</tbody>
</table>

*Based on logrank analysis

Conclusions: In men with PSAADT<12 months, PSAADT subgroups<7.5 months and PP ≥10 ng/ml are independent predictors of MFS, adjusted for pT stage and Gleason score. PP ≥10 ng/ml further define risk of M+ in BRPC with PSAADT<12 months. These data can assist physicians during discussions with patients regarding the risk of developing M1 disease and facilitate clinical trial design in this prevalent group of patients.

Legal entity responsible for the study: N/A

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Table: 820P

<table>
<thead>
<tr>
<th>PFS</th>
<th>OS</th>
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<tbody>
<tr>
<td>TLA*</td>
<td>HR (95% CI) p</td>
</tr>
<tr>
<td>&lt;563979</td>
<td>1.00</td>
</tr>
<tr>
<td>≥563979</td>
<td>1.13 (0.50-2.58) 0.762</td>
</tr>
<tr>
<td>MTV*</td>
<td>1.00</td>
</tr>
<tr>
<td>&lt;112</td>
<td>0.81 (0.33-2.00) 0.647</td>
</tr>
<tr>
<td>≥112</td>
<td>0.99 (0.38-2.56) 0.988</td>
</tr>
<tr>
<td>SUVmax*</td>
<td>1.00</td>
</tr>
<tr>
<td>&lt;50.00</td>
<td>2.04 (0.98-4.23) 0.056</td>
</tr>
<tr>
<td>≥50.00</td>
<td>3.38 (1.48-7.68) 0.004</td>
</tr>
</tbody>
</table>

Previous chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSAA* ng/mL</td>
<td>1.00</td>
<td>0.96 (0.50-1.84) 0.907</td>
</tr>
<tr>
<td>≥360</td>
<td>2.63 (1.42-4.87) 0.002</td>
<td></td>
</tr>
<tr>
<td>NLR</td>
<td>1.00</td>
<td>2.08 (1.08-4.00) 0.029</td>
</tr>
<tr>
<td>&lt;3</td>
<td>2.00 (1.08-3.68) 0.026</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>1.99 (1.04-3.82) 0.038</td>
<td></td>
</tr>
<tr>
<td>LDH, µU/mL</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>&lt;225</td>
<td>2.15 (1.07-4.34) 0.032</td>
<td></td>
</tr>
<tr>
<td>≥225</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>AR copy number</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>2.62 (1.26-5.47) 0.010</td>
<td></td>
</tr>
<tr>
<td>Gain</td>
<td>2.15 (1.02-4.52) 0.044</td>
<td></td>
</tr>
<tr>
<td>Median dsDNA concentration, ng/mL</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>&lt;38.5</td>
<td>2.04 (1.08-4.23) 0.056</td>
<td></td>
</tr>
<tr>
<td>≥38.5</td>
<td>0.69 (0.37-1.29) 0.243</td>
<td></td>
</tr>
<tr>
<td>After backward stepwise procedure</td>
<td>1.18 (0.60-2.33) 0.628</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: The decision to perform CT-PEt PSA in prostate cancer patients suspected to have recurrent or metastatic disease should be based on PSA levels. PSAADT is a significant marker for positive metastatic CT-PEt PSA uptake.

Legal entity responsible for the study: Avishay Sella

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Table: 820P

Combining functional imaging with circulating biomarker analysis to improve prognostication of metastatic castration-resistant prostate cancer (mCRPC)


Department of Oncology, Istituto Tumori della Rimagna (IRST), Meldola, Italy; Bioscences Laboratory, Istituto Tumori della Rimagna (IRST), Meldola, Italy; Nuclear Medicine Operative Unit, Istituto Tumori della Rimagna (IRST), Meldola, Italy; Unit of Biostatistic and Clinical Trial, Istituto Scientifico Romagnolo per lo Studio e la Cur a dei Tumori (IRST), Meldola, Italy; Treatment Resistance, Division of Molecular Pathology, The Institute of Cancer Research, Sutton, UK; Treatment Resistance, Division of Molecular Pathology, The Institute of Cancer Research, Sutton, UK

Background: Biomarkers for treatment personalization in mCRPC could improve patient outcomes. Multiple tests on blood have reported associations with worse outcome, including serum lactate dehydrogenase (LDH), chromogranin A (CgA), neutrophil-lymphocyte ratio (NLR) and more recently AR copy number (CN) in plasma DNA (Conteduca, Ann Oncol 2017). Biological data suggest an association between androgen receptor (AR) expression. We here aimed to integrate 11C-fluorocholine (FCH) uptake on PET/CT with plasma AR CN and other routinely obtained circulating biomarkers and evaluate associations with outcome.

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*Based on logrank analysis

Conclusions: In men with PSAADT<12 months, PSAADT subgroups<7.5 months and PP ≥10 ng/ml are independent predictors of MFS, adjusted for pT stage and Gleason score. PP ≥10 ng/ml further define risk of M+ in BRPC with PSAADT<12 months. These data can assist physicians during discussions with patients regarding the risk of developing M1 disease and facilitate clinical trial design in this prevalent group of patients.

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A polymorphism in the promoter of the FRAS1 gene is associated with metastatic prostate cancer


1Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; 2Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA; 3Department of Hematology and Medical Oncology, Harvard T.H. Chan School of Public Health, Boston, MA, USA; 4Biostatistics, Dana-Farber Cancer Institute, Boston, MA, USA; 5Channing Division of Network Medicine, Brigham Women’s Hospital, Boston, MA, USA; 6Epidemiology, Moffitt Cancer Center, Tampa, FL, USA; 7Department of General and Interventional Cardiology, University Heart Center Hamburg-Eppendorf, Hamburg, Germany; 8Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA, USA

Background: Inflammation and one of its mediating transcription factors, NF-kappa B signaling (NFkB) have been implicated in prostate cancer (PrCa) carcinogenesis. We sought to define whether germine gene polymorphisms that interact with NFkB signaling are associated with metastatic disease after prostatectomy (RP) or radiation (XRT) for localized disease.

Methods: Using a bioinformatics approach interrogating publicly available datasets, we defined a genome-wide functional association network specific to lethal PrCa. Of these, rs1910301 in the promoter region of FRAS1 was nominally associated with lethal disease in all 3 studies with similar size effects: the odds ratio (OR) for the allele was 1.40 (p = 0.02) in HSPH, 1.35 in ECOG/CbG (p = 0.04), and borderline significant in FH (OR 1.3, p = 0.07). Fixed effects meta-analysis of the three cohorts found a significant association: OR = 1.38 (95% CI: 1.15-1.66; p-value 0.005).

Conclusions: A SNP in the promoter region of FRAS1, which forms a gene unit with FREM2 and together regulate epidermal-basement membrane adhesion and cell migration, is associated with metastatic PrCa. FREM2 is an NFkB regulated gene and mutations in FREM2 and FRAS1 are associated with the Fraser syndrome. Further work is needed to determine the effect of rs1910301 on FRAS1 function and cellular adhesion and the metastatic process.

821P

Expression of steroid hormone transporter, SLC01B3, is mediated by a CBP/p300 regulatory mechanism in prostate cancer


1Genitourinary Malignancies Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA; 2Clinical Pharmacology Program, Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA

Background: Recent studies support the role of steroid hormone transporters in modulating intratumoral androgen concentrations, thereby promoting castration-resistant prostate cancer (mCRPC) progression. The organic anion polydrate 1B3 (OATP1B3) transporter is expressed de novo in prostate tumors and contributes to the transport of androgen into these cells. Polymeric variations in the SLC01B3 gene encoding OATP1B3 are related to clinical outcome in men with prostate cancer receiving androgen deprivation therapy (ADT) or taxanes. In a separate cohort, the same classifier predicted improved PSA response when pts were treated with a PARPi + ARBs vs. ARS alone. Here, we examined if OATP1B3 can have improved OS when receiving a common and inexpensive platinum chemotherapy.

Methods: 89 blood samples were collected from mCRPC pts prior to taxane Tx (n = 62) or a combination of taxane + platinum (T + P) (n = 27), and processed utilizing the Epic Sciences platform. Choice of therapy was at the discretion of attending physician without knowledge of CTC results. The percent of predicted GI cells per pt sample (%pGI) was calculated after single-cell characterization. Pts were followed for OS.

Results: Pts receiving a T + P combination had higher CTC burdens and lower PSA levels but otherwise showed similar pre-Tx characteristics to taxane-only pts. In a multivariate model containing %pGI, therapy class, and total CTC burden (to help correct for disease burden and severity), a significant interaction between the T + P combination and increasing %pGI, and increased OS (HR: 0.14; CI: 0.02 to 0.72, p = 0.018) was observed.

Conclusions: This is the first study suggesting that in a prospective setting with a balanced cohort, pts with high %pGI might have improved OS on taxanes with the addition of platinum agents. Prospective validation of the signature is planned. Legal entity responsible for the study: Epic Sciences

Funding: Epic Sciences


823P

Phenotypic circulating tumor cell (CTC) classifier of genomic instability (GI) associates with improved overall survival (OS) for metastatic castration-resistant prostate cancer (mCRPC) patients (pts) receiving platinum agents in addition to taxanes


1Genitourinary Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA; 2Translational Research, Epic Sciences Inc., San Diego, CA, USA

Background: The presence of GI has been associated with DNA Damage Response (DDR) genomics: mCRPC pts with DDR(-) can have treatment (Tx) efficacy with poly ADP ribose polymerase inhibitors (PARPi). Similar Tx benefit for DDR(-) pts has been observed with alkylating agents such as platinum Tx in small cohorts. However, obtaining and sequencing metastatic biopsies is currently not scalable for routine use in the clinic. Attaining accessibility, cost and time are resulting. We previously developed an imaging-based phenotypic classifier to predict presence of GI from individual CTC morphology and demonstrated that these pts had statistically worse OS when receiving androgen re- ceptor (AR) signaling inhibitors (ARSi) or Taxanes. In a separate cohort, the same classifier predicted improved PSA response when pts were treated with a PARPi + ARS vs. ARS alone. Here, we examined if GI(+) mCRPC pts can have improved OS when receiving a commonly available and inexpensive platinum chemotherapy.

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Results: Pts receiving a T + P combination had higher CTC burdens and lower PSA levels but otherwise showed similar pre-Tx characteristics to taxane-only pts. In a multivariate model containing %pGI, therapy class, and total CTC burden (to help correct for disease burden and severity), a significant interaction between the T + P combination and increasing %pGI, and increased OS (HR: 0.14; CI: 0.02 to 0.72, p = 0.018) was observed.

Conclusions: The results of this study suggest that in a prospective setting with a balanced cohort, pts with high %pGI might have improved OS on taxanes with the addition of platinum agents. Prospective validation of the signature is planned. Legal entity responsible for the study: MKSCC

Funding: Epic Sciences

Censoring the right endpoint of the distribution of time to event while estimating survival probabilities.

## Methods

### Study Design

A prospective, single-center, open-label, randomized, controlled trial was conducted. Patients were randomly assigned to receive either ABT-869 or placebo in a 1:1 ratio. The primary endpoint was time to disease progression (TTP), defined as the time from randomization to the date of disease progression or death from any cause.

### Randomization

Patients were stratified by baseline characteristics including age, performance status, and prior treatment history. Randomization was performed using a computer-generated, stratified, block randomization method.

### Treatment Regimen

Patients received either ABT-869 (250 mg orally once daily) or matching placebo in an open-label fashion. Treatment was continued until disease progression or unacceptable toxicity.

### Statistical Analysis

The primary endpoint was analyzed using the log-rank test and the Kaplan-Meier method. Secondary endpoints included overall survival (OS), quality of life (QoL), and safety.

## Results

The study enrolled 100 patients, of whom 50 were assigned to each treatment group. Median TTP was 7.2 months for the ABT-869 group and 4.9 months for the placebo group (p = 0.04). The median OS was 18.7 months for the ABT-869 group and 13.9 months for the placebo group (p = 0.01).

### Safety

The most common adverse events were diarrhea (42% vs 32%), nausea (36% vs 24%), and fatigue (26% vs 18%). No treatment-related deaths occurred in either group.

## Conclusion

ABT-869 significantly prolonged TTP and OS compared to placebo. The study demonstrates the efficacy and safety of ABT-869 as a treatment for metastatic castration-resistant prostate cancer.

## Acknowledgments

The study was supported by grant number 2019-2020 from the Spanish National Research Council (CSO2019-107761-REY). The authors thank all the patients and research teams involved in the study.

## References


Annals of Oncology

Results: 38 validated gmDDR were detected in 419 patients (9.1%), with 5 additional cases undergoing further validation studies. BRCA2 was the most frequently mutated gene (n = 14) followed by ATM (n = 8), BRCA1 (n = 4) and CHEK2 (n = 4). Characteristics at prostate cancer diagnosis (dx): 99% caucasian; median age 66y (41-92); Gleason <7 41% vs 5 59%; localized stage 35 vs stage IV 65%. Characteristics at mCPRC dx: median age 73y (43-94); ECOG 0-1 91% vs 2 9%; presence of visceral 8%, bone 87% and lymph node metastasis 46%; median baseline PSA 26.5ng/ml (<0.02-5198). Bone metastases were significantly more common at mCPRC dx in carriers (95% vs 80%, p = 0.04), as well as ALP >2 ULN (37% vs 19%, p = 0.03) and Albumine < 4g/dl (43% vs 21%, p = 0.02). No significant differences were observed between carriers and non-carriers in age at dx or mCPRC. Gleason, stage at dx, PSA, LDH, Hemoglobin, visceral or nodal metastases at mCPRC dx (p > 0.05).

Conclusions: This is the first study that reports the prevalence of gmDDR in a cohort of metastatic mCPRC patients.

Clinical trial identification: NCT03075735

Legal entity responsible for the study: Spanish National Cancer Research Centre (CNIO)

Funding: Spanish National Cancer Research Centre (CNIO)

Disclosure: All authors have declared no conflicts of interest.

B27P

Comprehensive characterization of BRCA1 and BRCA2 alterations in circulating tumor DNA and tumor tissue in men with prostate cancer: Implications for clinical care


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Background: Alterations in genes encoding for DNA damage repair (DDR) such as BRCA1 or 2—as detected by next generation sequencing (NGS)—can predict for sensitivity to PARP inhibitors or platinum-based chemotherapy in advanced prostate cancer (PC). Detection of these alterations either in tumor tissue or in circulating tumor DNA (ctDNA) in men with advanced PC is clinically actionable in certain clinical contexts. Previously, we reported the comprehensive molecular characterization of DNA DDR genes in 936 unique primary & metastatic PC specimens (Dalle’er, ASCO GU 2017) where 24.4% had at least 1 mutation in a DNA repair gene. We also reported that DNA DDR alterations were more common in metastatic vs. localized disease. We sought to expand this work by employing NGS in ctDNA as part of clinical care to ascertain the mutational status of BRCA1 and 2 in men with PC.

Methods: The nature and prevalence of BRCA1 and 2 alterations in ctDNA were determined from 207 men with PC through the Foundation ACT NGS assay. Mean depth of coverage was 696x. Similarly, BRCA1/2 alterations in 936 unique PC specimens were assessed as part of the Foundation One NGS assay. Mean depth of coverage was >500X.

Results: In ctDNA specimens from 207 men, 15 (7.2%) abnormal or likely deleterious BRCA1 (n = 4) and/or BRCA2 (n = 12) alterations consisting of 19 short variants and 2 rearrangements. One case had 4 variants in BRCA2 while 3 cases had 3 variants, of which 1 case had both BRCA1 and 2 variants. An additional 17 ctDNA samples (8.2%) abnormally harbored BRCA1/2 alterations categorized as variants of unknown significance (VUS). In the 936 tumor specimens, 118 (12%) had known or likely deleterious BRCA1 (n = 11) or BRCA2 (n = 107) alterations consisting of 4 rearrangements, 18 short variants, and 30 copy number variants. VUS were not available for tumor specimens.

Conclusions: Potentially actionable BRCA1 and/or BRCA2 alterations are detectable in ctDNA or tumor tissue in up to 15% of men with PC in this large dataset of specimens obtained in the course of clinical care. Employing plasma-based ctDNA NGS provides a clinically convenient means for assessing the status of DNA gene repair alterations comparable to that of tumor tissue.

Legal entity responsible for the study: University of California Davis Comprehensive Cancer Center and Foundation Medicine

Funding: None

Disclosure: R. Hartmaier, S.M. Ali: Employee of Foundation Medicine. All other authors have declared no conflicts of interest.

B28P

Durability of prostate cancer control in a randomized trial of optimal timing of dose escalated (76 Gy) radiation and 6 months ADT in prostate cancer patients

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Background: A pooled analysis of trials using conventional dose radiation (XRT) indicates 6 months androgen deprivation therapy (ADT) improves prostate cancer survival in Gleason 7 disease (D’Amico, JCO 2011). The benefit of ADT when used in combination with dose escalated XRT remains controversial. In EORTC 22991 trial 6 months ADT improved disease free survival at all XRT dose levels (Bolla, JCO 2016). We present long-term results of dose escalated XRT (76 Gy) in combination with 6 months ADT in the context of a Phase 3 Trial evaluating the optimal timing of ADT in combination with XRT.

Methods: 438 pts were entered on the trial. Inclusion criteria were cT1-T3, Gleason <8, PSA <30. Low risk pts were excluded. ADT consisted of 6 mo Total Androgen Blockade (TAB) with Goserelin and Bicalutamide. Pts were randomized to upfront XRT (day 1 of ADT) or XRT after 4 months ADT. Median follow-up is 12 yrs. 10 yr overall Survival (OS), Cause Specific Survival (CSS) PSA Disease Free Survival (DFS) and Local DFS were estimated using Kaplan-Meier (KM) method.

Results: Clinical characteristics are as follows: mean age 69, 69% cT1-T2A, 31% cT2B-T3, 75% Gleason 7, mean PSA = 10.7, cT2B-T3 protocol compliance: 96% of pts completed 6 mo TAB and 99% completed 6 mo Goserelin. 4% of patients stopped Bicalutamide early (3% due to Grade 3–4 reversible liver toxicity). 4% of patients developed late Gr 3 proctitis. 10 yr results: PSA DFS 83%, CSS 98%, OS 76%, and local DFS 95%. The results by treatment arm will be presented in the near future.

Conclusions: The durable DFS, local control and CSS support the benefit of 6 mo ADT in combination with Dose Escalated (76 Gy) XRT. The durable compliance, tolerance and toxicity data support this treatment approach. Potential survival benefits of ADT in intermediate risk prostate cancer will be evaluated by mature results from EORTC 22991 and RT0815 trials.

Clinical trial identification: OTT 01-01

Legal entity responsible for the study: Ottawa Hospital Research Institute

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Table: 829P Mean change in score from baseline for AAP (N = 46) vs ENZ (N = 59)

<table>
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<th>Month 3</th>
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<tr>
<td></td>
<td>AAP</td>
<td>ENZ</td>
<td>P value</td>
</tr>
<tr>
<td>Perceived cognitive impairments</td>
<td>Score difference</td>
<td>2.1 (42)</td>
<td>2.7 (53)</td>
</tr>
<tr>
<td></td>
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<td>AAP</td>
<td>ENZ</td>
</tr>
<tr>
<td></td>
<td>Odds ratio</td>
<td>% (n*)</td>
<td>% (n*)</td>
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<tr>
<td></td>
<td>0.47 (1.26, 1.00)</td>
<td>7.4 (1.26, 8.29)</td>
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<td>5.4 (41)</td>
<td>6.65 (2.79, 10.51)</td>
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<td>Fatigue interference</td>
<td>−0.4 (41)</td>
<td>0.3 (54)</td>
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<td>−0.7 (26)</td>
<td>0.07 (0.02, 0.28)</td>
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</table>

*Evaluable pts

Regression model estimates: Note: 7 pts (2 AAP, 5 ENZ) included in this intention-to-treat analysis switched treatment within the first 3 months; results were consistent in the per protocol analysis and censoring analysis.
28% of patients with BMI ≤30 and in 26% with BMI > 30, indicating no clear association with BMI (p = 0.7427). Cox model analyses also showed no clear influence on PSA progression of other anamnestic factors.

**Conclusions:** Patients in the LEAN study represent a real-life population receiving therapy with a GnRH agonist. Results show no clear influence of anamnestic factors on PSA progression.

**Clinical trial identification:** DRKS00005643

**Legal entity responsible for the study:** N/A

**Funding:** This study was funded by Hexal AG/Sandoz International GmbH.

**Disclosure:** B. Schmitz-Drüger: Consultant or assessor: Hexal, Janssen, Amgen Fees: Hexal, Jansen, Medac, B. Ottlinger: Consultant or assessor: Hexal Fees: Hexal Employment or position of leadership: Hexal, M. Studen: Holder of shares, stocks or funds: Hexal, Amgen Employment or position of leadership: Hexal.

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**Table: 831P**

<table>
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<th>Source</th>
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<th>Seizures</th>
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<th>Memory impairment</th>
<th>Anxiety</th>
<th>Insomnia</th>
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<tr>
<td>AAP</td>
<td>2267 (75%)</td>
<td>1.12 (0.89-1.40)</td>
<td>1.0 (0.99-2.01)</td>
<td>1.0 (0.99-2.01)</td>
<td>1.0 (0.99-2.01)</td>
<td>0.97 (0.77-1.23)</td>
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<td>0.97 (0.77-1.23)</td>
<td>0.97 (0.77-1.23)</td>
</tr>
<tr>
<td>ENZ PREVAIL &amp; AFFIRM</td>
<td>2914 (75%)</td>
<td>2.20 (0.89-1.29)</td>
<td>2.50 (1.67-1.77)</td>
<td>1.21 (0.86-1.47)</td>
<td>4.74 (0.79-2.67)</td>
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<td>1.21 (0.86-1.47)</td>
<td>1.21 (0.86-1.47)</td>
<td>1.21 (0.86-1.47)</td>
</tr>
</tbody>
</table>

*p < 0.05

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**832P**

**Influence of an international consensus conference on practice patterns in advanced prostate cancer (APC)**

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**Background:** Development of several agents and combinations in metastatic castrate-naïve (mCN) and castration-resistant (mCR) PC has led to uncertainty in best management approaches. The Advanced Prostate Cancer Consensus Conference (APCCC) 2017 convened to provide expert opinions on open questions.

**Methods:** 57 questions (Qs) selected from a sample of consensus Qs to be voted on at APCCC 2017 were administered as a pre- and post-conference survey to attendees. Matched responses before and after APCCC 2017 were compared to identify changes in attendees’ treatment preferences in APC.

**Results:** From 2/2017-4/2017, pre- and post-conference surveys from 120 attendees were collected mostly from medical oncologists (41.7%) and urologists (40.8%). Attendees reached a consensus ≥75% vote in the same pre- and post-meeting question in 10/57 Qs (17.5%). A < 75% consensus vote or ≥ 75% vote (or vice-versa) change was seen in 3 key areas: abiraterone or enzalutamide was more favored as first-line option in patients (pts) who progressed on docetaxel (56 months in mCNPC; 60 months pre- to 75.9% post-meeting), 2 years was the favored duration of osteo-osteo-targeted therapy in mCRPC (53.3% to 73.0%), and more next-generation imaging (MRI or PET/CT) was favored in mCRPC (12.7% to 24.1%) while CT and bone scan changed from 79.7% to 70.7% of votes. Consensus ≥75% votes was not reached in the majority of Qs, but not-ably there were more post-conference votes for: using a lower dose of cabazitaxel 20 mg/m² vs 25 mg/m² (24.2% to 32.8%), carboplatin in refractory mCRPC with DNA repair defects (27.5% to 42.2%), adding ADT to salvage XRT (29.1% to 49.1%), ≤3 metastases as a definition for oligometastatic PC (48.7% to 70.8%), recognition of ADT causing bone loss/fractures (57.4% to 66.4%), vitamin D + calcium in pts on ADT (62.6% to 71.7%), and osteo-osteo-targeted therapy in pts on ADT with osteopenia/osteoporosis (42.6% to 59.3%).

**Conclusions:** To the best of our knowledge, we are among the first to compare pre- and post-meeting questions that highlight interesting changes in provider preferences in APC management. Consensus conferences such as APCCC where expert opinions are discussed provide a unique learning experience and delineate key areas of controversy in APC where further study is needed.

**Legal entity responsible for the study:** The Advanced Prostate Cancer Consensus Conference

**Funding:** The Advanced Prostate Cancer Consensus Conference

**Disclosure:** S.K. Pal: Honoraria: Novartis, Medivation, Astellas Pharma Consulting or Advisory Role: Pfizer; Novartis, Aveo, Myriad Pharmaceuticals, Genentech, Eutelixis, Bristol-Myers Squibb, Curevac, Dendreon, Ferring, GlaxoSmithKline, Janssen Cilag, MaxiVAX SA, Millennium Pharmaceuticals, Novartis, Pfizer, Oncon, Roche, Sanofi-Aventis. All other authors have declared no conflicts of interest.
Postoperative radiation therapy after radical prostatectomy

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Background: To analyze the results of adjuvant and salvage radiotherapy after radical prostatectomy and to determine prognostic factors of biochemical relapse free survival (BRFS).

Methods: 302 patients were treated at our institution over a 12-year period. Overall survival and biochemical relapse free survival were calculated using Kaplan-Meier and multivariate Cox regression analysis was used to assess differences between groups.

Results: Mean age at diagnosis was 65 years (42-80). All patients underwent radical prostatectomy combined with pelvic lymphadenectomy in 47.1% of cases. Adjuvant RT was performed in 113 patients and salvage RT in 183 (9 for local recurrence). The distribution of patients by pt stage was pT2a-b (30.3%), pT2c (35%), pT3 (29%) and pT4 (2.3%). Upgrade in Gleason score between biopsy and prostatectomy was experienced by 46.9% of patients. Positive surgical margins were reported in 36.5% of cases. Neoadjuvant androgen ablation before surgery was given to 36.5%. Mean pre-RT PSA of 0.46ng/ml (0-12.8) and mean dosis to surgical bed was 74Gy (60-79Gy). Mean follow-up was 58.85 months (1-153 months). Overall survival at 5 and 10 years was 98.1% and 94.3%, respectively and BRFS at 5 and 10 years was 76.5% vs 61.8%, respectively. The timing of RT (ART vs SRT) and pre-RT PSA (<0.5mg/ml) were significant predictors of longer BRFS.

Conclusions: Postoperative radiation therapy provides excellent long-term overall survival with an acceptable BRFS. Pre-RT PSA <0.5mg/ml and adjuvant RT were predictors of better outcomes.

Legal entity responsible for the study: Hospital Ramón y Cajal
Funding: None
Disclosure: All authors have declared no conflicts of interest.

Randomized phase III trial of ipatasertib vs placebo, plus abiraterone and prednisone/prednisolone, in men with asymptomatic or mildly symptomatic previously untreated metastatic castrate-resistant prostate cancer (mCRPC)

I. de Bono1, S. Bracarda2, K. Chh,3, C. Massard4, D. Olmos5, S. Sandhu6, C.R. Steinberg7, T. Senders8,9, N. Xu9, T. Bane10,11, D. Maslyar1,1j,12, C.J. Sweeney3
1Division of Clinical Studies and Experimental Medicine, Institute of Cancer Research and The Royal Marsden Hospital, London, UK, 2Medical Oncology, Department of Oncology, Azienda USL Toscana Sud-Est, Instituto Toscana Tumori (ITT) and Ospedale San Donato, Arezzo, Italy, 3Clinical Trials Unit, BC Cancer Agency, Vancouver, BC, Canada, 4Early Drug Development, Department of Drug Development, Ipsen, 5Drug Safety, Ipsen, 6Phia, France, 7Prostate Cancer Clinical Research Unit, Spanish National Cancer Research Centre, Madrid, Spain, 8Department of Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia, 9Department of Oncology, San Camillo and Forlanini Hospitals, Roma, Italy, 10Late Stage Biomarker Development, Genentech Inc., South San Francisco, USA, 11Biostatistics - Oncology, Genentech Inc., South San Francisco, CA, USA, 12Product Development Oncology, Genentech Inc., South San Francisco, CA, USA, 13Medical Oncology Department, Dana-Farber Cancer Institute, Boston, MA, USA

Background: In a Phase Ib/II study, the small-molecule AKT inhibitor ipatasertib in combination with abiraterone and prednisone/prednisolone demonstrated an improved radiographic progression-free survival (rPFS) vs abiraterone and prednisone/prednisolone alone, with greater benefit in patients with phosphatase and tensin homolog (PTEN)-loss tumors. This randomized Phase III trial will evaluate the efficacy, safety and pharmacokinetics (PK) of ipatasertib vs placebo (both combined with abiraterone and prednisone/prednisolone) in patients with previously untreated mCRPC.

Trial design: Eligible patients must have untreated asymptomatic or mildly symptomatic mCRPC with progressive disease by Prostate Cancer Clinical Trials Working Group 3 criteria for hormone-sensitive disease and have been previously treated with abiraterone and have no evidence of disease progression on docetaxel or cabazitaxel. Eligible patients (N = 880) will be randomized 1:1 to receive 600 mg darolutamide BID or placebo BID, both with best supportive care, until disease progression. Patients will be stratified by country, WHO performance status (0, 1 vs 2), presence/absence of visceral metastases, enzalutamide vs abiraterone prior to chemotherapy, and planned start of therapy after the last taxane dose (<35 days vs ≥35 days). The primary endpoint is rPFS at 12 weeks after treatment initiation. The secondary endpoints are rPFS, time to PSA progression, time to symptomatic/crincine progression, event-free survival, overall survival, PSA response (30%, 50%, 90%, and best), duration of PSA response (30%), adverse events, and fatigue. The rPFS rate at 12 weeks after treatment initiation will be compared between the two treatments using a one-sided test statistic using the Kaplan–Meier method. Recruitment is ongoing, with the first patient randomized on 20.04.2017.

Clinical trial identification: NCT02933801
Legal entity responsible for the study: Swiss Group for Clinical Cancer Research (SAKK)
Funding: Bayer HealthCare Pharmaceuticals Inc.
Disclosure: S. Gillessen: Advisory Boards: AAA International, Active Biotech, Astellas, Bayer, Bristol-Myers Squibb, Curacav, Dermomed Corporation, Ferring, Glaxo Smith Kline, InnoCinco Pharmaceuticals, Janssen Cilag, MaxiVAX, Millennium
Pharmaceuticals, Novartis, Pfizer, Orion, Roche, Sanofi Aventis R. Cathomas: Advisory Board for Bayer, Jansen, Astellas, Sanofi, Pfizer, Novartis, Roche, Amgen, AstraZeneca, BMS, MSD. All other authors have declared no conflicts of interest.

836TP

The TRITON clinical trial programme: Evaluation of the PARP inhibitorrucaparib in patients (Pts) with metastatic castration-resistant prostate cancer (mCRPC) associated with homologous recombination deficiency (HRD)


Background:
Recent data show that ∼20% of pts with mCRPC have a germline or somatic alteration in either BRCA1, BRCA2 or ATM (homologous recombination [HR] genes) (Robinson et al. Curr Opin Genet Dev 2016;23:1, 16). mCRPC trials targeting PARP inhibitors (PAPR) in pts with a deleterious germline or somatic BRCA1, BRCA2 or ATM mutation (per local and/or central testing) have shown improved progression-free survival (PFS) in mCRPC pts with HRD. The triplet combination of ATR, PARP and BRCA1 inhibition was recently shown to have a reasonable safety profile.

Trial design: TRITON3 is a phase 2 study evaluating rucaparib 600 mg BID in pts (n=160) with mCRPC who have a deleterious germline or somatic BRCA1, BRCA2 or ATM mutation (per local and/or central testing). Pts with tumours with an alteration in any of 12 additional prespecified HR genes (eg, BARD1, RAD51 or PALB2) may be enrolled in an exploratory cohort. Pts must have progressed on AR-directed therapy and on 1 prior taxane-based chemotherapy for mCRPC. The primary endpoint of TRITON3 is response rate (modified RECIST v.1.1). Circulating tumor DNA will also be collected pre- and post-therapy to explore resistance mechanisms.

Clinical trial identification: NCT02959284

Legal entity responsible for the study: Clovis Oncology, Inc.

Funding: Clovis Oncology, Inc.


Bioscience Stock and Other Ownership Interests: Clovis Oncology. S. Shetty: A. Goloskori: Employment: Clovis Oncology Stock and Other Ownership Interests: Clovis Oncology. C.J. Ryan: Consulting or Advisory Role: Bayer, Millennium Honoraria or Consultancy: Astellas Pharma Rebane, Buxade. INO Biosciences, Karopharm Therapeutics, Novartis. H. Scher: Advisory: Endo, Foundation Med, OncologySTAT, Palmetto GBA, Takeda, Ventana Med Sys, MDV Spk Bureau: WebMD Hon: Chugai Consul/Travel: AZ, Astellas, BMS, Celgene, Endoextx, Exelixis, Ferring, GNE, PFE, Sanofi, Janssen, Takeda, WIBB/Compericus Grp. All other authors have declared no conflicts of interest.

837TP

Phase I study of apalutamide (ARN) plus abiraterone acetate (AA), docetaxel (D) in patients (pts) with metastatic castrate-resistant prostate cancer (mCRPC)

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Background: Androgen receptor (AR) targeted therapy is the mainstay of treatment for PC, with potent AR signaling inhibitors and CYP17 inhibitors leading to improved survival. Taxanes are the only chemotherapy class to demonstrate a survival benefit in prospective randomized studies. Docetaxel (D), inhibits AR trafficking from the cytoplasm to the nucleus via stabilizing microtubule, suggesting D may complement AR pathway targeted therapies. Recent randomized studies showing ≥2 year median survival benefit in men treated with the combination of effective direct AR-targeted therapies combined with D, suggesting that “vertical” AR pathway blockade in which combinations of AR-directed therapies with complementary mechanisms of action are more effective than sequential use (Sweeney NEJM 2015, James Lancet 2016). Two phase 3 trials are testing the combination of AR signaling inhibitors and CYP17 inhibitors. The safety of combining D with AA in pts with mCRPC was demonstrated in the COU-AA-206 (Tagawa Eur Urol 2016). Combinations of therapies targeting different pathways have the potential to improve efficacy.

Trial design: A multicenter phase I dose-escalation study will be conducted to determine the maximum tolerated dose (MTD) of ARN (novel AR signaling inhibitor) combined with AA (CYP17 inhibitor) and D (taxane) in chemotherapy-naive mCRPC pts with ECOG performance status 0-2. Following determination of MTD, a cohort expansion at the recommended Phase 2 dose will occur. Starting doses are 120 mg/day ARN with 100 mg/day AA, D 75 mg/m2 every 3 weeks, and prednisone 5 mg BID. Upon completion of D, pts may continue ARN and AA. The primary endpoint is the safety and tolerability of ARN when dosed with AA and D. Tumor tissue will be collected prospectively to evaluate exploratory biomarkers predictive of response and resistance. In addition, pre- and post-treatment circulating tumor cells will be interrogated for AR localization and AR splice variants. Circulating tumor DNA will also be collected pre- and post-therapy to explore resistance mechanisms.

Clinical trial identification: NCT02913196

Legal entity responsible for the study: Well Cornell Medical College Funding: Janssen Scientific Affairs, LLC


838TP

ARASENS: A phase 3 trial of darolutamide in males with metastatic hormone-sensitive prostate cancer (mHSPC)

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2Department of Surgery, University of Montreal Hospital Center/CICIM, University of Montreal, QC, Canada.
3Urology, Westmead Hospital, School of Medicine, The University of Sydney, Sydney, NSW, Australia.
4Department of Urology, University of Queensland, Brisbane, Queensland, Australia.
5Urology, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden.
6Urology, Harvard Medical School, Boston, MA, USA.
7Urology, Cancer Centre, Catholic University of Louvain (UCL), Brussels, Belgium.
8Clinical Statistics, Bayer AG, Berlin, Germany.
9Urology, Cancer Research Centre, University of Southern Denmark, Odense, Denmark.

Background: While androgen-deprivation therapy (ADT) demonstrates antitumor activity in mHSPC with prolonged disease control, resistance ultimately occurs and patients die of castration-resistant PC (CRPC). Approximately 10-50% of PC subjects develop CRPC in <5 yr. Chemohormonal therapy per ESMO guidelines is recommended as first-line treatment of metastatic, castration-naive disease in men fit enough for chemotherapy. Darolutamide (DAMD-201) is a unique investigational oral androgen
receptor (AR) antagonist that binds the AR and AR mutants (eg, W742L and F877L) with high affinity and selectivity, thus, inhibiting receptor function and dihydrotestosterone binding with negligible blood-brain barrier penetration. In the phase 1/2 ARADUS and ARAFOR trials, darolutamide had antitumor activity and was well tolerated in men with mCRPC (Fizazi et al. Lancet Oncol 2014; Massard et al. Eur Urol 2016). As a result of this encouraging activity in mCRPC, the ARASENS trial is evaluating darolutamide plus standard ADT + docetaxel in men with mHSPC.

Trial design: This international, randomized, double-blind, placebo-controlled, phase 3 trial (NCT02799602) is being conducted in 23 countries. 1300 men with newly diagnosed mHSPC will be randomized 1:1 to either 600 mg (2 × 300 mg) darolutamide + docetaxel + placebo, both with ADT + docetaxel (6 cycles after randomization), and stratified by extent of disease and alkaline phosphatase levels. Key inclusion criteria are confirmed PC with documented metastases, age ≥ 18 years, Eastern Cooperative Oncology Group performance status 0-1, and no prior chemotherapy. The primary objective is to show superior overall survival with darolutamide + placebo, both with ADT + docetaxel. Secondary endpoints include time to progression, time to first skeletal-related event, and disease control rate.

Clinical trial identification: NCT02799602

Legal entity responsible for the study: Bayer

Funding: Funded by Bayer. Darolutamide was discovered at Orion Corporation and is being jointly developed with Bayer.


**839TP**

A phase II clinical trial of radium-223 activity in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) with asymptomatic progression while on abiraterone acetate or enzalutamide besides AR-V7 mutational status (EXCAAPE)


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Background: Radium-223 is indicated for pts with mCRPC with symptomatic bone metastases. Biomarkers for radium-223 treatment and its correlation with AR-V7 splice variant are both under research. The aim of this study is to assess the activity and safety of radium-223 stratified by AR-V7 status in asymptomatic pts who have progressed while on abiraterone acetate or enzalutamide treatment.

Trial design: This is a single-arm, multicenter, phase IIA clinical trial. Pts will receive radium-223 at a dose of 55 kBq per kg, given at 4-week intervals for 6 intravenous injections, until progression or unacceptable toxicity. We will screen for AR-V7 splice variant and CTCa number after inclusion, at the end of treatment and at progression. We predict that the number of AR-V7+ pts will be ≥ 25% at inclusion. Major inclusion criteria are: (1) mCRPC according to standard Prostate Cancer Working Group (PCWG2)-2 criteria; (2) asymptomatic according to Brief Pain Inventory short form; (3) ≥ 24 weeks of prior treatment with abiraterone acetate or enzalutamide; (4) adequate organ function and performance status. The primary endpoint is the radiographic progression-free survival (rPFS) according to the PCWG2-2 criteria. A total of 52 pts were predefined for the primary analysis using the one arm log-rank test. In both cohorts, we test the null hypothesis that true median rPFS is ≤ 3 months versus the alternative hypothesis that it is ≥ 6.3 months. The one-sided type I error was 0.025 for both AR-V7 subgroups. A sample size of 13 pts is needed in the AR-V7+ subgroup to attain 80% power. In accordance with the expected ratio between cohorts, we will include 39 pts in AR-V7- subgroup. The secondary objectives are to investigate the safety of the treatment, to determine the association between AR-V7 status and tumor response and to establish the relationship between circulating tumor cell number with radium-223 activity. Trial registration number is NCT03002220. Date of registration was 20/10/2016. First patient included on 20/12/2016.

Clinical trial identification: NCT03002220, Initial Release Date: 20/Oct/2016

Legal entity responsible for the study: Medica Scienia Innovation Research-MEDSIR

Funding: Bayer Hispania S.L.


**840TP**

Stereotactic ablative radiotherapy (SABR) for oligoprogressive metastatic castration-resistant prostate cancer (mCRPC) during abiraterone therapy: A phase I study

U. Eimmermeier1, S. Cheng1, K. Zukatsynski2, P. Cheung3

1 Medical Oncology, Dottore Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada. 2 Medicine and Radiology, McMaster University, Hamilton, ON, Canada. 3 Radiation Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada.

Background: Despite recent therapeutic advances, there is a continuing need for novel prostate cancer treatment strategies. Some men with mCRPC may present at some points with oligometastases, a state between loco-regional and widespread metastatic disease with metastases being limited both in number and location. This oligometastatic state exists de novo, can be induced by effective systemic therapies, or may present under the picture of oligoprogression. The latter is a situation where ≤ 3-5 metastatic tumor sites progress, while all other metastases are controlled by ongoing systemic therapy. The typical practice would be to change systemic therapy at this point. SABR is an emerging treatment option for oligometastatic or oligoprogressive malignancies. Used for this indication SABR may improve survival and delay the need to change systemic therapy. However, some patients may derive limited benefit only because of early and widespread metastatic progression following SABR. While there are no validated biomarkers to predict these two scenarios in date, circulating tumor DNA (ctDNA) is a minimally invasive and highly informative biomarker platform for identifying molecular changes associated with treatment outcome.

Trial design: In the absence of published evidence on the use of SABR for oligoprogressive mCRPC in men undergoing abiraterone therapy, we are conducting a phase I study to determine the incidence of acute and late toxicities (primary endpoint) associated with delivering SABR to all oligoprogressive metastatic sites in 30 men with mCRPC on abiraterone. We also aim to collect preliminary efficacy data of such an approach as secondary endpoints (eg time to biochemical and radiological or/and symptomatic progression following SABR). Using conventional imaging, eligible mCRPC candidates will be identified based on ≤ 5 SABR amenable progressive metastatic lesions (≤ 5 in any one organ system) while all other metastases remain stable or are responding to abiraterone therapy. Before SABR, we will collect ctDNA to perform gene copy number and mutational analyses of prostate cancer relevant genes as a means to predict sustained responses to SABR.

Legal entity responsible for the study: Sunnybrook Research Institute, Toronto, ON, Canada

Funding: Janssen Inc., Canada

Disclosure: U. Eimmermeier: Research support for this study and paid advisory board meetings of the manufacturer of abiraterone. All other authors have declared no conflicts of interest.

**841TP**

A randomized phase II study comparing cabazitaxel/prednisone to cabazitaxel alone for second-line chemotherapy in men with metastatic castrate resistant prostate cancer (mCRPC): CABACARE

C. Busquets1, D. Bosso2, S. De Placido3, G. Di Lorenzo4

1 Medical Oncology Unit, Federico II Hospital, Naples, Italy. 2 Department of Clinical Medicine and Surgery, University Federico II, Naples, Italy.

Background: In the TROPIC study, cabazitaxel (CAI), administered with prednisone (PNI) 10 mg daily, showed significant advantage in OS and PFS in patients (pts) progressing during or after docetaxel (DOC) treatment. Similar to DOC, CAI has been approved in combination with daily PNI, although the contributing role of PNI to...
efficacy and safety has been poorly investigated. Corticosteroids have a variety of effects, which may be either favourable, mediated by adrenal androgen and cytokine suppression, or detrimental, because of adverse events associated with long-term use, promiscuous activation of AR, immunosuppression, activation of AR variants highly sensitive to PDN even at low concentrations. Moreover PDN acts as a CYP3A4 inducer, affecting clearance of taxanes. It has been shown that AR point mutations are rare in therapy-naive pts but occur in 15–49% of CRPC pts and can increase AR affinity for a wide range of steroids. Over 100 mutations have been described. In the CHAARTED trial DOC was safely administered without daily PDN showing important clinical benefits in OS, PFS, and time to CRPC; Safety data for CAB without PDN are lacking. AR-V7 positivity and RB loss/inactivation have been identified as potentially implicated in progression with next-generation targeted agents. We also would like to prospectively assess their role as predictive biomarkers of CAB activity.

**Trial design:** CABACARE is a randomized, phase II, open-label, multicenter study comparing CAB at 25 mg/m2 q21 plus daily PDN (10 mg) vs CAB at 25 mg/m2 q21 alone in mCRPC pts progressed during or after DOC treatment. The study is designed to test non-inferiority in terms of PFS, according to PCWG-2, of CAB alone vs CAB plus PDN, assuming that the two arms are equally effective. Each arm will enroll 110 pts. Main secondary objectives are: safety, QoL, pain assessment, overall response rate (ORR), PSA response, time to PSA progression, time to radiological progression; OS; and association of skeletal related events (SRE). The influence of ARv7 and RB status on CAB activity will also be evaluated.

**Clinical trial identification:** EUDRACT 2016-005251-25

**Legal entity responsible for the study:** Consorcio Oncotec

**Funding:** Sanofi-Aventis

**Disclosure:** C. Buserba: Consultant for Sanofi. Research support to institution from Sanofi, Astellas, Quercken Pharmaceuticals. Travel expenses from Janssen-Cilag, S. De Placido: Research Support to Institution from Sanofi, Astellas, Quercken Pharmaceuticals. G. Di Lorenzo: Consultant for Sanofi. Research Support to Institution from Sanofi, Astellas, Quercken Pharmaceuticals.

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**References:**

D. Lorente Estelles, J. Puente1, A. Medina1, R. Lozano Mejorada4, L. Rivero4, M.I. Facheco1, M.I. Sáez4, M. Pulats Rodríguez1, E. Fernandez Parra1, B. Borrega Garcia1, B. Pérez Valderrama1, E. Gallardo Diaz1, R. Villatoro1, R. Morales Barrera15, S. Vazquez Estebane3, A. Pinto Marin14, J.A. Contreras Ibáñez15, M. Romero Laorden1, E. Castro Marcos15

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**Background:** The evolution of CRPC is heterogeneous, and despite progress in its management, several new agents approved for CRPC, we are still far from being able to predict which group of patients might benefit from a particular strategy. Therefore, the identification of new predictive and prognostic biomarkers is urgently needed. The evolution of CRPC is heterogeneous, and despite progress in its management, several new agents approved for CRPC, we are still far from being able to predict which group of patients might benefit from a particular strategy. Therefore, the identification of new predictive and prognostic biomarkers is urgently needed. The evolution of CRPC is heterogeneous.
PROSENZA: Prospective multi-centre study of prognostic factors in castration resistant prostate cancer (CRPC) patients treated with enzalutamide (ENZ)


1Medical Oncology, Centro Oncológico de Galicia, A Coruña, Spain, 2CNIO-IBIMA Genitourinary Research Unit, Hospital Universitario Virgen de la Victoria y Regional de Málaga, Málaga, Spain, 3Prostate Cancer Clinical Research Unit, Spanish National Cancer Research Centre, Madrid, Spain, 4Medical Oncology, Vall d’Hebron University Hospital, Barcelona, Spain, 5Medical Oncology, Hospital Universitario de Canarias, Santa Cruz de Tenerife, Tenerife, Spain, 6Medical Oncology, Hospital Costa del Sol, Málaga, Spain, 7Medical Oncology, Hospital Universitario San Espíritu, Patna de Málaga, Spain, 8Radiation Oncology, Hospital Universitario Ramón y Cajal, Madrid, Spain, 9Medical Oncology, HUF A Hospital Universitario Fundación Alcorcon, Alcorcon, Spain, 10Medical Oncology, Hospital Althaia Manresa, Manresa, Spain, 11Medical Oncology, Hospital Universitario 12 de Octubre, Madrid, Spain, 12Medical Oncology, H. San pedro de Alcántara, Córdoba, Spain, 13Medical Oncology, Consorci Sanitari del Maresme, Mataró, Spain, 14Medical Oncology, Hospital de San Pedro, Logroño, Spain, 15Prostate Cancer Unit, Spanish National Cancer Center, Madrid, Spain

**Background:** CRPC is a heterogeneous disease, and despite new agents approved, the optimal sequence of treatment remains unclear, far from personalised medicine that may offer the maximal benefit for the patient. For that reason, our aim is the identification of new biomarkers in CRPC patients treated with conventional therapy.

**Trial design:** PROSENZA is a prospective multicentre observational study in metastatic CRPC designed to explore biomarkers in patients treated with ENZ. Key inclusion criteria: a) histological confirmation of prostate cancer; b) documented criteria (PCWG2) for CRPC; c) availability of tumour tissue; d) candidate for standard treatment with ENZ. Primary end point: to study the prognostic value for overall survival (OS) of the detection of androgen receptor splicing variant 7 (AR-V7) and/or amplification of AR (ARþ) in peripheral blood in this cohort. Secondary end points: a) to analyse the correlation between PSA response and AR-V7 and/or ARþ; b) to evaluate the correlation between radiological response and AR-V7 and/or ARþ; c) to study changes in AR-V7 frequency and/or ARþ pre and post ENZ; d) to analyse and correlate the prognostic role of AR-V7 and ARþ with other biomarkers as testosterone serum levels, PTEN loss or TMPRSS-ERG fusions. Exploratory outcomes: a) to validate in this cohort prognostic nomograms described for CRPC; b) to validate the prognostic role of the expression signature described by Olmos et al (Lancet Oncol 2012) in peripheral blood; c) to explore new somatic and germinal variants in peripheral blood and tissue associated to dissemination, response and resistance to ENZ. PROSENZA is part of the PROCURE Biomarkers network, a multicentric Spanish platform for biomarkers discovery in CRPC. 187 patients will be accrued to provide appropriate statistical power to detect at least 71 events (deaths) to analyse the main outcome. Currently, 48 centres are active for recruitment and 54 patients have been included. Blood samples are collected before, during and after progression to ENZ. Prospective data collection will be linked. This study may help to incorporate new biomarkers in clinical practice and improve the selection of therapy in mCRPC.

**Clinical trial identification:** NCT02922218

**Legal entity responsible for the study:** Spanish National Cancer Research Centre

**Funding:** Partially funded by Astellas

**Disclosure:** A. Medina: Honoraria from Astellas. All other authors have declared no conflicts of interest.
Phase III randomized, open-label study to evaluate the efficacy and safety of sorafenib-pazopanib versus pazopanib or sorafenib in the treatment of metastatic renal cell carcinoma (SWITCH-II)

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1Dept. of Urology, Technical University of Munich, Klinikum rechts der Isar, Munich, Germany, 2Dept. of Urology, University Hospital Tübingen, Tübingen, Germany, 3Dept. of Urology, University Clinics Berlin, 4Dept. of Urology, University Hospitals Munich, Munich, Germany, 5Dept. of Urology, University Clinics Münster, Münster, Germany, 6Dept. of Urology, University Hospital Heidelberg, Heidelberg, Germany, 7Dept. of Urology, University Clinics Dresden, Dresden, Germany, 8Dept. of Urology, University Clinics Ulm, Ulm, Germany, 9Dept. of Oncology, TumorCenter Sieckhusen, Tübingen, Germany, 10Dept. of Oncology, Rainer-Franz-Josef-Spital, Vienna, Austria, 11Dept. of Oncology, Sparrne Ziekenhuis, Hoofddorp, Netherlands, 12Biostatistics, IOMEDICO AG, Freiburg, Germany

Background: The previous SWITCH-I study explored the two possible sequences of Sorafenib and Sunitinib for the treatment of advanced/metastatic renal cell carcinoma (mRCC) and showed similar total progression-free-survival (IPFS) and overall survival (OS) times. This trial compared the sequential therapy with the multikinase inhibitors Sorafenib (So) followed by Pazopanib (Pa) or vice versa in mRCC patients (pts).

Methods: This multicentre, randomised phase 3 study assessed the sequential use of So-Pa versus Pa-So in pts with mRCC without prior systemic therapy. Pts were randomised to So 400 mg twice daily followed by Pa 800 mg once daily (So-Pa) in case of progression or intolerable toxicity or vice versa (Pa-So). The primary endpoint was non-inferiority of IPFS with So–Pa compared to Pa–So, assessed from randomisation to progression or death during second-line therapy defined as hazard ratio (HR) < 1.25 as a one-sided 95% confidence interval (CI). Main secondary endpoints included OS, total time to progression (TTP), disease control rate (DCR), 1st-line and 2nd-line PFS as well as safety and tolerability.

Results: 377 pts were randomised (So-Pa: n = 189; Pa-So: n = 188). Median IPFS was 8.6 mo (95% CI 7.7-10.2) for So-Pa and 12.9 mo (95% CI 10.8-15.2) for Pa-So with a HR of 1.36 (upper limit of one-sided 95% CI 1.68). Therefore, non-inferiority of So-Pa in regard to IPFS was not met. However, marked statistical differences were noted in favour of Pa-So in total TTP, 1st-line PFS and DCR but not for OS and 2nd-line PFS. In the So-So arm 106/189 (56%) received Pa as 2nd line and for the Pa-So arm 87/188 (46%) received So as 2nd line. The most frequent any grade treatment-emergent first-line adverse events for So were diarrhoea (56%), fatigue (37%) and hand-foot skin reaction (35%) and for Pa diarrhoea (60%), hypertension (48%) and fatigue (45%).

Conclusions: Non-inferiority of the sequence So-Pa compared to Pa-So in terms of the primary endpoint IPFS was not met. However, superiority of the sequence Pa-So over So-Pa for IPFS was not proven either, since the study design was computed with a HR of < 1.225 as a one-sided 95% CI.

Clinical trial identification: NCT01638466, first received May 4, 2012

Legal entity responsible for the study: Technische Universität München

Funding: Bayer Vital GmbH and in part GSK-Novartis


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Impact of tumor mutation burden on nivolumab efficacy in second-line urothelial carcinoma patients: Exploratory analysis of the phase II checkmate 275 study

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Background: Nivolumab, a programmed death (PD)-1 inhibitor, demonstrated efficacy in a single-arm phase II study in patients (pts) with metastatic or surgically unresectable urothelial carcinoma (UC) (CheckMate 275, Sharma et al. 2017). The current analysis explores the potential association between pretreatment tumor mutation burden (TMB) and response to nivolumab.

Methods: Tumor DNA from pretreatment archival tumor tissue and matched whole blood samples was profiled by whole exome sequencing. TMB was defined as the total number of missense somatic mutations per tumor, and was evaluated as a continuous variable and by tertiles (missense count: high ≥167, medium 85–166, low <85). Cox models were used to explore the association between TMB and progression-free survival (PFS) and overall survival (OS); and logistic regression for objective response rate (ORR). Tumor PD-1 ligand 1 (PD-L1) expression was assessed by Dako PD-L1 immunohistochemistry 28-8 assay and was categorized as <1%, 1%–5%, 5%–25%, >25%.

Results: 139 (51%) of 270 pts had evaluable TMB. Baseline characteristics, ORR, PFS, and OS were similar between all treated pts and the TMB subgroup. ORR, PFS and OS in all pts and TMB/PD-L1 subgroups are shown in the Table. TMB showed a statistically significant positive association with ORR (P=0.002) and PFS (P=0.005), and a strong association with OS (P<0.001), even when adjusted for baseline PD-L1 expression, liver metastasis status, and serum hemoglobin. High TMB had the greatest impact on survival in pts with <1% PD-L1 expression (Table).

Conclusions: These exploratory findings suggest that TMB may enrich for response to nivolumab and may provide complementary prognostic/predictive information beyond PD-L1. Further analyses in randomized trials are warranted to define the prognostic/predictive value of TMB in the context of other biomarkers in UC pts treated with immunotherapy.

Clinical trial identification: NCT02387996

Legal entity responsible for the study: Bristol-Myers Squibb

Disclosure: M.D. Galasky: Received research funding from Bristol-Myers Squibb, Novartis, and Merck and has served on advisory boards for Genentech, Merck, EMD-Serono, and AstraZeneca. A. Saci: Reports being an employee of Bristol-Myers Squibb during the conduct of the study. A. Azrilevich: Reports being an employee of the sponsor, Bristol-Myers Squibb. C. Horak: Reports being an employee and stockholder of Bristol-Myers Squibb. A. Lambert: Reports employment and stock owner from Bristol-Myers Squibb.

Table: 848PD ORR, PFS and OS: All patients and TMB/PD-L1 subgroups

<table>
<thead>
<tr>
<th>Table: 848PD</th>
<th>ORR, %</th>
<th>PFS, months median</th>
<th>OS, months median</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pts N = 270</td>
<td>20.0 (95% CI) 15.8</td>
<td>2.00 (1.87–2.63)</td>
<td>8.57 (6.05–11.27)</td>
</tr>
<tr>
<td>TMB subgroup N = 139</td>
<td>20.1 (1.87–3.02)</td>
<td>7.23 (5.72–11.63)</td>
<td></td>
</tr>
<tr>
<td>TMB high N = 47</td>
<td>31.9 (1.87–NR)</td>
<td>11.63 (5.82–NR)</td>
<td></td>
</tr>
<tr>
<td>TMB medium N = 46</td>
<td>17.4 (1.68–3.65)</td>
<td>9.66 (4.76–NR)</td>
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<tr>
<td>TMB low N = 46</td>
<td>10.9 (1.84–3.15)</td>
<td>5.72 (4.21–11.30)</td>
<td></td>
</tr>
</tbody>
</table>

ORR based on blinded independent review committee assessment CI = confidence interval; NR = not reached.
Comparison of tumor mutational burden (TMB) in relevant molecular subsets of metastatic urothelial cancer (MUC)

1Medical Oncology, City of Hope, Duarte, CA, USA 2Medical Oncology, Huntsman Cancer Institute, Salt Lake City, UT, USA 3Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA 4Medical Oncology, Cambridge, MA, USA 5Pathology, Albany Medical Center, Albany, NY, USA

Methods: DNA was extracted from 40 microns of FFPE sections from 2024 consecutive patients with MUC. Comprehensive genomic profiling (CGP) was performed on hybridization-captured, adaptor ligation based libraries to a mean coverage depth of 888X for up to 315 cancer-related genes plus 37 introns from 14 genes frequently rearranged in cancer. The CGP assay included base substitutions (SUB), INDELs, copy number alterations (CNA) and fusions/rearrangements. TMB was determined on 1.2 million Mb of sequenced DNA; results are reported for the overall cohort and in subsets segregated separately by presence or absence of FGFR3, ERBB2/3, PIK3CA and CDKN2A/B alteration.

Results: 2024 consecutive pts (1457:567 M:F) with MUC were assessed with a median age of 67 years. Median TMB in the overall cohort was 7.2 mutations/Mb. FGFR3, ERBB2/3, PIK3CA, and CDKN2A/B alteration were identified in 23%, 14%, 4%, 19% and 37% of pts, respectively. TMB was significantly different in pts segregated based on ERBB2/3 alteration (P = 1.8x10^-14), PIK3CA alteration (P = 1.7x10^-7), and ERBB3 alteration (P = 0.01). ERBB2/3 and FGFR3 genomic alterations (GAs) were significantly mutually exclusive, while FGFR3 and PIK3CA GAs significantly co-occurred with PIK3CA and CDKN2A/B. Further differences in CGP amongst these subsets will be presented at the meeting.

Table: 849PD

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>ORR</th>
<th>Median PFS (95% CI)</th>
<th>Median OS (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Entire cohort</td>
<td>212</td>
<td>18.4%</td>
<td>1.97 (1.87-2.46)</td>
<td>8.74 (5.58-NR)</td>
</tr>
<tr>
<td>CD8low</td>
<td>106</td>
<td>11.3%</td>
<td>1.84 (1.71-1.94)</td>
<td>5.72 (4.3-8.74)</td>
</tr>
<tr>
<td>CD8high</td>
<td>106</td>
<td>25.5%</td>
<td>3.12 (2.04-4.14)</td>
<td>11.30 (10-3-NR)</td>
</tr>
<tr>
<td>EMTlow</td>
<td>106</td>
<td>23.6%</td>
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</tr>
<tr>
<td>CD8low EMThigh</td>
<td>42</td>
<td>40.5%</td>
<td>5.52 (3.45-NR)</td>
<td>NR (11.3-NR)</td>
</tr>
</tbody>
</table>

Table: 850PD Outcomes with nivolumab

<table>
<thead>
<tr>
<th>Group</th>
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<th>ORR</th>
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<td>CD8low EMThigh</td>
<td>42</td>
<td>40.5%</td>
<td>5.52 (3.45-NR)</td>
<td>NR (11.3-NR)</td>
</tr>
</tbody>
</table>

Conclusions: Given the proposed correlation between TMB and IO response, these data may inform the utility of combination strategies. Specifically, given higher TMB in pts with ERBB2/ERBB3 or PIK3CA alteration, combination studies exploring IO with TT directed at these targets may be warranted.

Legal entity responsible for the study: Sumanta K. Pal, MD

Funding: None


Epithelial-mesenchymal transition (EMT), T cell infiltration, and outcomes with nivolumab (nivo) in urothelial cancer (UC)

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1Medicine, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA 2Oncology, Bristol-Myers Squib, Princeton, NJ, USA

Background: The presence of tumor infiltrating lymphocytes has been associated with a higher objective response rate (ORR) to PD-1/PD-L1 blockade. Across a variety of cancers, high EMT gene expression correlates with increased T cell infiltration. The impact of these interrelated processes on outcomes with PD-1/PD-L1 blockade has not been defined.

Methods: The TCGA UC cohort (n = 405) was utilized to determine the relationship between EMT gene signature (sig) expression (200 genes in MSigDB) and infiltrating T cell abundance (ITA). ITA was inferred using mRNA expression of 144 T cell genes. A phase 2 trial of irinotecan in metastatic UC (CheckMate 275, n = 212) was used to determine the impact of EMT sig (HTG EdgeSeq) and CD8 expression (IHC) on ORR, progression-free survival (PFS), and overall survival (OS).

Results: In the TCGA cohort, EMT sig correlated with ITA (CC = 0.60, p = 2e-16). The correlation remained significant after correction for sample purity (CC = 0.37, p = 1e-14) and UC molecular subtype (p = 1e-3). In the CheckMate 275 cohort, EMT sig correlated with CD8 expression (CC = 0.29, p = 2e-05). The impact of EMT sig and CD8 expression on outcomes is shown (Table). Higher CD8 expression was associated with longer PFS (p = 0.003) and OS (p = 0.01). There was a significant interaction between EMT sig and CD8 (P = 0.038; OS, p = 0.064); in CD8high tumors, ORR, PFS, and OS were worse in EMTsig vs EMTlow.

Table: 850PD

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>ORR</th>
<th>Median PFS (95% CI)</th>
<th>Median OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire cohort</td>
<td>212</td>
<td>18.4%</td>
<td>1.97 (1.87-2.46)</td>
<td>8.74 (5.58-NR)</td>
</tr>
<tr>
<td>CD8low</td>
<td>106</td>
<td>11.3%</td>
<td>1.84 (1.71-1.94)</td>
<td>5.72 (4.3-8.74)</td>
</tr>
<tr>
<td>CD8high</td>
<td>106</td>
<td>25.5%</td>
<td>3.12 (2.04-4.14)</td>
<td>11.30 (10-3-NR)</td>
</tr>
<tr>
<td>EMTlow</td>
<td>106</td>
<td>23.6%</td>
<td>2.10 (1.87-3.65)</td>
<td>8.74 (6-5-NR)</td>
</tr>
<tr>
<td>EMThigh</td>
<td>106</td>
<td>13.2%</td>
<td>1.91 (1.81-2.46)</td>
<td>6.57 (4.96-NR)</td>
</tr>
<tr>
<td>CD8low EMTlow</td>
<td>64</td>
<td>15.6%</td>
<td>2.04 (1.84-3.52)</td>
<td>NR (6.57-NR)</td>
</tr>
<tr>
<td>CD8low EMThigh</td>
<td>42</td>
<td>40.5%</td>
<td>5.52 (3.45-NR)</td>
<td>NR (11.3-NR)</td>
</tr>
</tbody>
</table>

Conclusions: While much effort has been focused on “turning cold tumors hot” as a strategy to improve the efficacy of PD-1/PD-L1 blockade, a large proportion of “hot tumors” do not respond. Among “hot” UC, EMTsig tumors are associated with a lower ORR to nivo and shorter PFS and OS. These findings substantiate EMT as a potential mechanism of immune escape and raise the possibility of co-targeting EMT and PD-1/PD-L1 in “hot” UC.

Clinical trial identification: NCT02387996

Legal entity responsible for the study: Matthew Galasky

Funding: Bristol-Myers Squib

Disclosure: M.D. Galasky: Received research funding from Bristol-Myers Squib, Novartis, and Merck and has served on advisory boards for Genentech, Merck, EMD-Serono and AstraZeneca. A. Saci and P.M. Szabo. Employees of Bristol-Myers Squib. All other authors have declared no conflicts of interest.
Results from subgroup analyses of KEYNOTE-045 demonstrate that treatment-related AEs of grade (pembro), 44% (paclitaxel), 54% (docetaxel), and 51% (vinflunine) experienced 61% (pembro), 88% (paclitaxel), 92% (docetaxel), and 91% (vinflunine) of pts. 15% was similar between pembro and each of the chemo agents. ORR (95% CI) was 21% among the 4 groups. Median follow-up was 14 mo (range, 10-22 mo). Pembro was
AstraZeneca, Novartis, Pfizer, Agensys, outside the submitted work. Q. Zhu, B. Ding, C. Kaiser: Employee and stock owner - Genentech, Inc. J.E. Rosenberg: Reports non-financial support from Roche-Genentech, during the conduct of the study; personal fees from AstraZeneca, Novartis, Pfizer, outside the submitted work. A.R. Reuter: Employee - Novartis, outside the submitted work. G.M. Macwindy: Employee and stock owner - Genentech, Inc. M.L. Hudes: Employee and stock owner - Genentech, Inc. J. Bywater: Employee - Novartis, outside the submitted work. K.M. Krajewski 5, H. Jacene 6, J. Bellmunt 1, M.M. Pomerantz 1, L.C. Harshman 1, T.K. Choueiri 1
1Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, 2Medical Oncology, Moores Cancer Center in San Diego, San Diego, CA, USA, 3Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA, USA, 4Genitourinary Cancer Center, Massachusetts General Hospital Cancer Center, Boston, MA, USA, 5Radiology, Dana-Farber Cancer Institute, Boston, MA, USA, 6Nuclear Medicine, Dana-Farber Cancer Institute, Boston, MA, USA

Background: BM occur in 30% of patients (pts) with mRCC and are associated with symptomatic skeletal events (SSE) and worse outcomes with vascular-endothelial growth factor (VEGF)-targeted agents. Rad is a bone-seeking a-emitter that targets BM. We investigated the safety, efficacy and bone turnover markers (BTM) of Rad. Rad was administered monthly for up to 6 infusions. The primary endpoint was BTM. Secondary endpoints included safety, SSE rate, time to SSE, objective response rate (ORR), narcotic use and survival.

Results: Of the 30 pts, 76% had clear cell histology, 17% were IMDC poor risk and 33% had liver metastases. Prior SSEs were reported in 100% and 65% of pts in the P and S cohorts, respectively. 1 pt had received denosumab. Median changes in BTM at cycle 2 and 4 compared to baseline are summarized in Table and show declines in all BTMs. Best ORR by RECIST was partial response (PR) in 13% and stable disease (SD) 47%. Achieving > -50% decline in PINP at cycle 2 was associated with PR and SD (Fisher’s exact p-value 0.01). Median treatment duration was 3.6 mo (IQR 1.5, 5.3). Progression-free survival was 8.2 mo (95%CI 5.6, NR) and 4.6 mo (95%CI 2.1, NR) in pts treated with P and S. Overall survival was 11.9 mo (95%CI 7.8, NR) and 8.7 mo (95%CI 6.6, NR), respectively. Overall rate of SSE on study was 47%, 67% in the P cohort (median time to SSE 6.3 mo (95%CI 3.6, NR)) and 27% in the S cohort (median time to SSE NR (95%CI 6.6 mo, NR)). There was no dose-limiting toxicity. The rate of treatment-related grade ≥ 3 toxicity was 39.3% including 3.6% grade 3 anemia.

Achieving 50% decline in PINP at cycle 2 was associated with PR and SD (Fisher’s exact p-value 0.01). Median treatment duration was 3.6 mo (IQR 1.5, 5.3). Progression-free survival was 8.2 mo (95%CI 5.6, NR) and 4.6 mo (95%CI 2.1, NR) in pts treated with P and S. Overall survival was 11.9 mo (95%CI 7.8, NR) and 8.7 mo (95%CI 6.6, NR), respectively. Overall rate of SSE on study was 47%, 67% in the P cohort (median time to SSE 6.3 mo (95%CI 3.6, NR)) and 27% in the S cohort (median time to SSE NR (95%CI 6.6 mo, NR)). There was no dose-limiting toxicity. The rate of treatment-related grade ≥ 3 toxicity was 39.3% including 3.6% grade 3 anemia.

Conclusions: Rad combined with P or S is safe and well tolerated. All BTMs significantly declined with Rad combined with P or S suggesting biologic activity in mRCC with BM. Randomized trials are needed to evaluate the role of Rad on SSE prevention in these pts.

Clinical trial identification: Clinical trial information NCT024066321

Legal entity responsible for the study: Dana-Farber Cancer Institute

Funding: Bayer

Disclosure: R.R. McKay: Research funding from Bayer and Pfizer. M.D. Michaelsen: Advisory board of Genentech, Pfizer, Dendreon, Sotio, Genentech, Merck, Bristol-Myers Squib, Jannsen. T.K. Choueiri: Received institutional research funding from Pfizer, exelixis, Bristol-Myers Squib, Novartis, and has an advisory role at Pfizer, Novartis, Genentech, Merck, Bristol-Myers Squib and Bayer. The remaining authors have no disclosures. All other authors have declared no conflicts of interest.

Table: 854PD

<p>| Table: 852PD Key baseline characteristics and outcomes in patients treated beyond 1st RECIST v1.1 PD |</p>
<table>
<thead>
<tr>
<th>ATEZO TREATMENT BEYOND PD (n = 137)</th>
<th>NO ATEZO TREATMENT BEYOND PD (n = 83)</th>
<th>NO ATEZO BEYOND PD (n = 83)</th>
<th>Other systemic tx (n = 19)</th>
<th>No systemic tx (n = 64)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median age</td>
<td>66 yr</td>
<td>67 yr</td>
<td>65 yr</td>
<td>68 yr</td>
</tr>
<tr>
<td>Male sex</td>
<td>80%</td>
<td>71%</td>
<td>63%</td>
<td>73%</td>
</tr>
<tr>
<td>Primary site: bladder</td>
<td>75%</td>
<td>75%</td>
<td>79%</td>
<td>73%</td>
</tr>
<tr>
<td>ECOG PS 0</td>
<td>43%</td>
<td>31%</td>
<td>42%</td>
<td>28%</td>
</tr>
<tr>
<td>Mets. visceral/liver</td>
<td>82%/27%</td>
<td>87%/41%</td>
<td>84%/42%</td>
<td>88%/41%</td>
</tr>
<tr>
<td><strong>Response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-PD RECIST v1.1 ORR</td>
<td>12%</td>
<td>1%</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Post-PD RECIST v1.1 ORR</td>
<td>1%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Overall survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median follow-up duration (event/pt rate)</td>
<td>21.2 mo (70%)</td>
<td>20.0 mo (92%)</td>
<td>19.0 mo (90%)</td>
<td>20.0 mo (92%)</td>
</tr>
<tr>
<td>OS, median</td>
<td>12.8 mo</td>
<td>3.6 mo</td>
<td>8.8 mo</td>
<td>2.9 mo</td>
</tr>
<tr>
<td>18-mo OS</td>
<td>33.4%</td>
<td>3.9%</td>
<td>10.5%</td>
<td>1.7%</td>
</tr>
<tr>
<td>ppOS, median</td>
<td>8.6 mo</td>
<td>1.5 mo</td>
<td>6.8 mo</td>
<td>1.2 mo</td>
</tr>
<tr>
<td>12-mo ppOS</td>
<td>37.1%</td>
<td>2.7%</td>
<td>10.5%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Treatment-related AEs, % (exposure-adjusted rate)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Gr: on/before PD (total of 18 pt-yr)</td>
<td>66% (512 per 100 pt-yr)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>All Gr: after PD (total of 31 pt-yr)</td>
<td>53% (234 per 100 pt-yr)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Gr 3-4: on/before PD (total of 43 pt-yr)</td>
<td>9% (28 per 100 pt-yr)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Gr 3-4: after PD (total of 60 pt-yr)</td>
<td>9% (22 per 100 pt-yr)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Table: 854PD

<table>
<thead>
<tr>
<th>BTM</th>
<th>Baseline (IQR) N = 30</th>
<th>% change at cycle 2 median (IQR) N = 21</th>
<th>% change at cycle 4 median (IQR) N = 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone-specific alkaline phosphatase (BALP)</td>
<td>11 (9, 16) ug/mL</td>
<td>−17 (-36, -7)</td>
<td>−23 (-32, -7)</td>
</tr>
<tr>
<td>Osteocalcin (OC)</td>
<td>16 (12, 19) ng/mL</td>
<td>−33 (-45, -21)</td>
<td>−49 (-52, -31)</td>
</tr>
<tr>
<td>N-terminal propeptide of procollagen type I (PINP)</td>
<td>46 (30, 66) ug/mL</td>
<td>−57 (-63, -29)</td>
<td>−63 (-69, -44)</td>
</tr>
<tr>
<td>C-terminal cross-linked telopeptide of type I collagen (CTX)</td>
<td>432 (210, 595) pg/mL</td>
<td>−37 (-51, -1)</td>
<td>−34 (-49, -22)</td>
</tr>
<tr>
<td>N-terminal cross-linked telopeptide of type I collagen (NTX)</td>
<td>15 (11,21) nM BCE</td>
<td>−28 (-43, -7)</td>
<td>−28 (-43, -15)</td>
</tr>
</tbody>
</table>
Adjuvant sunitinib (SU) in patients (pts) with high risk renal cell carcinoma (RCC): Safety and therapy management in S-TRAC trial


1Genitourinary Malignancies Branch, Center for Cancer Research, National Cancer Institute National Institutes of Health, Bethesda, MD, USA, 2Medical Oncology, Nova Cancer Research Foundation, Las Vegas, NV, USA, 3Medical Oncology, National Cancer Institute National Institutes of Health, Bethesda, MD, USA, 4Medical Oncology, National Cancer Institute National Institutes of Health, Bethesda, MD, USA, 5Medical Oncology, R&D Global Early Development, EMD Serono, Inc., Billerica, MA, USA, 6Medical Oncology, The Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA, 7Medical Oncology, University Hospitals Leuven, Leuven, Belgium, 8Hematology/Oncology, Henry Ford Hospital, Detroit, MI, USA, 9Medical Oncology, University Hospitals Leuven, Leuven, Belgium, 10Biostatistics, EMD Serono, Inc., Billerica, MA, USA, 11Medical Oncology, The Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA, 12Medical Oncology, University Hospitals Leuven, Leuven, Belgium, 13Research & Development, EMD Serono, Inc., Billerica, MA, USA, 14Medical Oncology, Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL, USA

Background: pts with locoregional RCC at high risk (≥T3 and/or N+) of tumour recurrence post nephrectomy treated with adjuvant SU (50 mg daily; schedule 4/2) had significantly longer disease-free survival (DFS) vs. placebo (PBO, HR 0.76; 95% CI, 0.59–0.98; P = 0.03). We report safety and therapy management data.

Methods: Reasons for SU treatment discontinuation (TDC), dose reduction (RED), dose interruption (INT), and pts TDC due to AEs by cycle, were summarized. Median time to SU TDC was calculated.

Results: Of the 615 pts enrolled, 306 were treated with SU at a median (range) daily dose of 45.9 (8.9–52.6) mg. 71% of pts remained on SU treatment for 9 months (me and 56% completed the full 1 year treatment. Most common reasons for TDC were AEs (28.1%) and relapse (7.2%) in SU arm, and relapse (19.4%) and AEs (5.9%) in PBO arm. Common AEs leading to TDC, RED and INT are summarized in the Table. TDC due to AEs cycles 1,3,6 and 9, respectively 7.8%, 3.3%, 2.6% and 4.6% in SU arm, and 0.3%, 1.3%, 0.3% and 0% in PBO arm. In the 86 pts who did SCU, median time to TDC was 4.5 mo. Median time to first RED and INT in SU-treated pts was 2.9 and 3.0 mo, respectively. Mean change from baseline in most PBO measures including Global Health Status for SU vs PBO was not clinically meaningful (difference, -4.76; 95% CI, -6.82, -2.71). More data, including time on RED/INT, time to onset of AEs, and the impact of AEs on pts quality of life, will be presented.

Table: 855PD Most common AEs leading to TDC, dose RED and INT*

<table>
<thead>
<tr>
<th>Treatment DC</th>
<th>Dose RED</th>
<th>Dose INT</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE, % SU PBO</td>
<td>AE, % SU PBO</td>
<td>AE, % SU PBO</td>
</tr>
<tr>
<td>Pne</td>
<td>4.2</td>
<td>11.8</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.0</td>
<td>3.9</td>
</tr>
<tr>
<td>Anemia</td>
<td>1.3</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1.0</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1.0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Many of the AEs leading to DC and INT were grade 1/2 TDC

Conclusions: No new safety signals were identified with sunitinib use in the adjuvant RCC setting. Effective therapy management, including dose RED/INT if necessary, is important as it optimizes the possibility of receiving effective treatment.

Clinical trial identification: NCT00357674

Legal entity responsible for the study: Pfizer

Funding: Pfizer

Disclosure: M. Staehler: Received honoraria, consulting fees, and research grants from Pfizer, Bayer, GSK, Roche, Bristol-Myers Squibb, Novartis, Ettelux and AVEO. R.J. Motzer: Received consulting fees from Pfizer, Novartis, Eisai and Entasai. D.J. George: Received honoraria & consulting: Dendreon, Sanofi, Bayer, consulting: Medivation, Merck, Genentech, Clovis, grants: Genentech, Novartis, Janssen, Astellas, Celldex, Acerta, grants & consulting: Ettelux, Pfizer, Sanofi, Innocrin Pharma, Bristol-Myers Squib. H.S. Pandha: Received honoraria for advisory work from ipsen and Eisai. F. Donskov: Received research funding from Pfizer, Novartis, and GSK. B. Escudier: Received consulting fees from Pfizer, Bristol-Myers Squib, Ipsen, EU-Pharma, and Novartis, and honoraria from Bayer, Pfizer, Genentech, Novartis, Bristol-Myers Squib, Eisai, Acellon and Ipsen. A.J. Pantuck: A. Pantuck has received consulting fees from Pfizer. L. Deannuntis, H. Bhattacharyya, X. Lin, M. Lechuga and L. Serfass.
Pembrolizumab (pembro) as first-line therapy in cisplatin-ineligible advanced urothelial cancer (UC): outcomes from KEYNOTE-052 in senior patients (pts) with poor performance status

Role: Honoraria, AstraZeneca; Consulting/Advisory, Merck, AstraZeneca.

Background: UC is most often seen in senior pts, in whom age-related comorbidities such as renal dysfunction and poor performance status (PS) preclude standard first-line cisplatin treatment. In the phase 2 KEYNOTE-052 trial (NCT02335424), first-line pembrolizumab had clinically meaningful antitumor activity (ORR, 24%) and was well tolerated in cisplatin-ineligible pts with UC. Results from the subgroup of pts who were considered senior (≥65 yr or ≥75 yr) and had ECOG PS ≥2 are presented.

Methods: Pts were cisplatin ineligible and had advanced UC, measurable disease (per RECIST v1.1), ECOG PS 0-2, and no prior systemic chemotherapy. Pts received pembrolizumab 200 mg Q3W. Radiographic imaging was performed at wk 9, then Q6W for the first 6 mos and Q12W thereafter. The primary end point was ORR (RECIST v1.1, independent radiology review).

Results: Of 370 pts, 302 (82%) were ≥65 yr, 179 (48%) were ≥75 yr, 120 (32%) were ≥65 yr and ≥75 yr, and 78 (21%) were ≥65 yr and ECOG PS ≥2. Median follow-up was 5 mo. ORR (95% CI) was similar to that reported in the overall study population regardless of age cuttoff (Table). Pts who did not achieve an ORR had ≥25% response. We are studying the safety and efficacy of sacituzumab govitecan (IMMU-132), an anti-Trop-2/SN-38 antibody-drug conjugate, in pts with UC refractory to other therapies.

Conclusions: Results from subgroup analyses of senior pts with poor PS in KEYNOTE-052 confirm that first-line pembrolizumab elicits clinically meaningful responses consistent with the overall study population. Pembrolizumab is well tolerated in cisplatin-ineligible pts with UC, including those who are senior with poor PS.

Clinical trial identification: NCT02335424; January 7, 2015

Legal entity responsible for the study: Merck & Co., Inc.

Funding: Merck & Co., Inc.


Table: B57F Efficacy Outcomes

<table>
<thead>
<tr>
<th>65 y or ≥75 y</th>
<th>65 and ECOG PS 2</th>
<th>65 y and ECOG PS 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % (95% CI)</td>
<td>23 (19-28)</td>
<td>23 (17-30)</td>
</tr>
<tr>
<td>CR</td>
<td>4 (2-7)</td>
<td>2 (1-4)</td>
</tr>
<tr>
<td>PR</td>
<td>19 (15-24)</td>
<td>21 (15-27)</td>
</tr>
<tr>
<td>6-mo PFS, %</td>
<td>30%</td>
<td>27%</td>
</tr>
</tbody>
</table>

B8SF Sacituzumab govitecan (IMMU-132) for patients with pretreated metastatic urothelial cancer (UC): interim results

Background: Pts with metastatic UC have limited therapy options. Immune checkpoint inhibitors (CPI) are now given to patients with advanced UC, but only about 25% respond. We are studying the safety and efficacy of sacituzumab govitecan (IMMU-132), an anti-Trop-2/SN-38 antibody-drug conjugate, in pts with UC refractory to other therapies.

Methods: In this phase II trial study (NCT01631552), pts with metastatic UC who were progressed after ≥1 prior systemic therapy were treated with IMMU-132 at 10 mg/kg on days 1 and 8 of 21-day cycles, until progression or unacceptable toxicity. All intention-to-treat (ITT) pts, including those who relapsed/progressed after CPI therapy, were eval-

Results: 41 pts (39±2F, median age 68 y, range 50-91) were enrolled (RE = 36%). ECOG PS 0-1 (median of 3 (range 1-6) prior therapies, including 34±1 platinum and 13±1 CPI regimens. Metastatic sites: lymph node 68%, lungs 54%, liver 32%, bone 27%, overall visceral disease, 31±1 (76%). Pts received a median of 12 (range 1-58) doses. ORR in the ITT population was 34% (14±1 (C.3), 13 PR); ORR was 39% in the RE group, including 5/13 (39%) with liver mets); 14 SD (39%); 8 PD (20%); and 5 evaluable. In responders, 13/14 had prior platinum, 8/14 (57%) ≥3 prior therapies, and 4 of 13 PR (4/13 in the RE group (31%), while IMMU-132 was ≥2 line of therapy in 11/13 pts). Median time to response: 1.9 mos. Median duration of response: 12.9 mos (95%CI, 3.1-12.9), with 8/14 continuing therapy. Clinical benefit rate (CR+PR+SD≥6 mos) was 44% 56% for SD ≥ 4 mos. In the 41 ITT pts, median PFS and OS are 7.2% (95% CI, 5.0-10.7) and 15.5 mos (95% CI, 9.8-11.2), respectively. Grade ≥3 adverse events ≥5% were 28% neutropenia, 9% febrile neutropenia, 9% fatigue, 9% anemia, 6% diarrhea.

Conclusions: With an ITT ORR of 34%, PFS of 72 mos, OS of 15.5 mos, and duration of response of 12.9 mos in 41 unselected pts with advanced pretreated UC (median of 3 prior therapies), these interim results show IMMU-132 is a promising agent in pts relapsed/refractory to chemotherapy and immune checkpoint inhibitors.
859P Anti-tumor activity of the pan-FGFR inhibitor rogaratinib in patients with advanced urothelial carcinomas selected based on tumor FGFR mRNA expression levels


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Background: Fibroblast growth factor receptor (FGFR) signaling is deregulated in urothelial carcinoma (UC). Rogaratinib is an oral inhibitor of FGFRs 1-4 with demonstrated antitumor activity in bladder cancer xenograft models. We report the results from a rogaratinib phase 1 trial expansion cohort in UC patients selected based on FGFR1-3 mRNA tumor overexpression and/or of presence of activating mutations in the FGFR3 gene.

Methods: Patients with locally advanced or metastatic UC who have progressed or ineligible for standard therapy were screened for high FGFR1-3 mRNA expression levels by RNA in situ hybridization (RNAscope®) and Nonspecific® assays utilizing fresh or archival FFPE tumor specimens. FGFR3-activating mutations were evaluated by a PCR based assay (Qiagen). Patients were treated with rogaratinib 800mg BID on a continuous 28-day schedule.

Results: Biopsies from a total of 109 patients with advanced UC were screened, with 42.3% found to be FGFR positive; of which 87% due to FGFR3 mRNA overexpression, 4% FGFR1, and 9% mixed FGFR isoform mRNA expression. Co-occurrence of FGFR3-activating mutations and high FGFR3 mRNA expression was seen in 8% of patients. Among 20 patients with UC treated with rogaratinib, 16 (73%) had tumor shrinkage in target lesions with 9 (45%) showing tumor shrinkage of more than 20% and 6 (30%) having a partial response (PR). Disease control rate (CR+PR+SD+D+CR=12w+) was 75%. Three patients with a PR had elevated tumor FGFR3 mRNA levels without corresponding genomic alterations. The most common any grade toxicities included fatigue 83%, neutropenia 75%, anemia 63%, alopecia 50%, elevated AST 46%, constipation and nausea 42% each and thrombocytopenia 36%.

Conclusions: GE exceeded the threshold for efficacy in this trial. The endpoints of ORR, OS and PFS compare favorably to the commonly used regimens in this setting which include such as sunitinib. Further study is warranted for response, with an ORR of 43%. All 24 pts were evaluable for toxicities; 10 evaluable pts, 2 had a CR, 10 had a PR, 5 had SD and 1 had PD. The objective response rate (ORR) was 63%. Overall survival (OS) 14.9 months (5.3, 16.1). Duration of response (DOR) was 4.6 months (range: 0.5, 15.0). Among the first 21 pts 7 had a PR and 2 had a CR and 5 were invalidable for response, with an ORR of 43%. All 24 pts were evaluable for toxicities; the most common any grade toxicities included fatigue 83%, neutropenia 75%, anemia 63%, alopecia 50%, elevated AST 46%, constipation and nausea 42% each and thrombocytopenia 36%.

861P Expression of long non-coding RNA MF2-A51 is a strong predictor of recurrence in sporadic localized clear-cell renal cell carcinoma


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Background: Improved patient stratification is a challenge in adjuvant clear-cell renal cell carcinoma (ccRCC) trials. Long non-coding RNAs (IncRNAs) are genome-wide regulators with potent prognostic value. We aimed to predict risk of ccRCC recurrence based on IncRNA expression from two independent cohorts.

Methods: Identification of prognostic IncRNAs was performed in a training set of 351 samples of localized ccRCC from the Cancer Genome Atlas, using Cox regression based on a false discovery (FDR) and overall survival. Functional annotation and differential expression was performed according to IncRNA expression. The validation cohort included 187 localized ccRCC patients. Gene expression was studied by qRT-PCR. Kaplan-Meier estimators and Cox regression models were used for survival and multi-variate analyses. Primary endpoint was DFS.

Results: MF2-A51 was best candidate IncRNA in the developmental study. Its expression was associated with immune response genes expression. In the validation cohort, MF2-A51 expression was associated with shorter DFS (HR for relapse: 3.5, p < 0.0001), independently from Leibovich recurrence classification and grade. Combined with Leibovich classification, MF2-A51 status improved prediction of recurrence, with a c-index of 0.70 compared to 0.67 for MF2-A51 alone and 0.66 for Leibovich classification alone. In patients with aggressive tumors (Leibovich ≥ 5), MF2-A51 expression was associated with a dramatically increased risk or relapse (HR 12.16, p < 0.0001) compared to patients with undetectable MF2-A51 who had ultimately favorable outcomes. MF2-A51 expression was also correlated with high tumor burden.
Conclusions: MF22-AS1 is a potent predictor of recurrence in localized ccRCC. Combined with historical classifications, it provides a highly accurate patient stratification that may be useful in adjuvant settings.

Legal entity responsible for the study: Gabriel G Malouf, MD, PhD. Fondation Avec & Hopital Salpétrière, Department of Medical Oncology, Paris, France

Disclosure: None

Funding: Annals of Oncology abstracts

Table: 863P

<table>
<thead>
<tr>
<th>Pembrolizumab n = 35</th>
<th>Pembrolizumab + acalabrutinib n = 40</th>
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</thead>
<tbody>
<tr>
<td><strong>Safety</strong>, n (%) (excluding events after cross over)</td>
<td></td>
</tr>
<tr>
<td>Any grade 3-4 AE</td>
<td>17 (49)</td>
</tr>
<tr>
<td>Any treatment-related grade 3-4 AE</td>
<td>6 (17)</td>
</tr>
<tr>
<td>Any grade 3-4 SAE</td>
<td>12 (34)</td>
</tr>
<tr>
<td>Any treatment-related 3-4 SAE</td>
<td>0 (0)</td>
</tr>
<tr>
<td>AE leading to study drug discontinuation</td>
<td>7 (20)</td>
</tr>
<tr>
<td>Grade 5 AE</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Treatment-emergent AEs, n (%) (any grade, ≥30% of all pts)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>16 (46)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>13 (37)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (20)</td>
</tr>
<tr>
<td>Anemia</td>
<td>7 (20)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10 (29)</td>
</tr>
<tr>
<td><strong>EF cacy</strong></td>
<td></td>
</tr>
<tr>
<td>ORR, % (95% CI) [n/N]</td>
<td>Overall population</td>
</tr>
<tr>
<td>PD-L1+ population</td>
<td>23 (8, 45) [5/22]</td>
</tr>
<tr>
<td>Median PFS, mo (95% CI)</td>
<td>1.6 (1.4, 4.2)</td>
</tr>
<tr>
<td>Median OS, mo (95% CI)</td>
<td>11.4 (5.7, NE)</td>
</tr>
<tr>
<td>12 mo OS, % (95% CI)</td>
<td>44.1 (27.2, 59.8)</td>
</tr>
</tbody>
</table>

AE, adverse event; CI, confidence interval; mo, month; NE, not estimable; ORR, overall response rate; PFS, progression-free survival; SAE, serious adverse event; OS, overall survival.
Between Jun 2015 and Jan 2016, 75 pts were treated with P (n = 35) or PA (n = 40); cross over, n = 10. Median age, 66 y; men, 76%; ECOG PS 0-1; 97% median prior therapies, 2 (range, 1-4). In P/PA median (mos) time on study treatment, 2.96/ 1.94; median follow-up, 11.26/1.1. Grade 3-4 treatment-emergent AEs (9%) ≥15% of P or PA was 16% (in P) and fatigue (23%), increased alanineaminotransferase (23%), urinary tract infection (18), and anemia (15) in P. There were 3 fatal AEs in PA; hem- optysis and sepsis (unrelated); pneumonia (P-related); ORR was 26% (CR, 9%) with P and 20% (CR, 10%) with PA. Median PFS was similar between treatment arms; median OS was 11.4 and 6.3 mos in P vs PA (Table). Most pts (69%) had PD-L1 + tumors; ex- pression was not associated with improved ORR (Table).

Conclusion: Most pts tolerated the study treatment, although P/PA-treated pts had grade 3-4 AEs. Acalabrutinib plus pembrolizumab did not improve ORR over pembrolizumab alone in pts with mUC, regardless of PD-L1 status.

Clinical trial identification: NCT0351739

Legal eligibility responsible for the study: Acrata Pharma

Funding: Acrata Pharma

Disclosure: T. Zhang: Stock ownership: Capio Biosciences; Consulting/Advisory Role: Bayer, GI Therapeutics; Research Funding: Janssen, Acrata Pharma, Pfizer, Merrimack.


R64P

Long non-coding RNAs are differentially expressed between bladder cancer subtypes

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1Department of Urology, University Medical Center Ljubljana, University Medical Center Ljubljana, Slovenia. 2Department of Urology, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany.

Background: The recent identification of molecular bladder cancer subtypes by whole transcriptome studies showed similarities to molecular breast cancer phenotypes. We here validate several subtypes with a sensitive 36 gene microarray and analyse relevant lncRNA for their differential expression.

Methods: RNA has been extracted from chemotherapy-naive muscle-invasive bladder cancer (MIBC) after radical cystectomy (follow-up: 12 years, n = 48). A multiple marker gene panel has been quantified with the microarray technology. In all validation of the classifier genes on 170 MIBCs has been performed. All squamous carcinoma were excluded. lncRNAs were analyzed in a clustering-independent assessment. Multivariate analyses were performed by a Cox proportional hazards model.

Results: 36 consensus genes were generated by Venn diagrams based on the Mannheim, Lund, Chungbuk and MDA cohorts. This minimal set of genes generated 3 stable clusters: basal, luminal and infiltrated. The subtype specific assessment of 14 lncRNAs relevant in bladder cancer showed a highly subtype specific expression for 9 lncRNAs. The infiltrated subtype was characterized by an activated p53 downstream signature, showed an overexpression of SRA1 and MEG3 (p < 0.003) - the latter is known for promoting the expression of TP53. The lncRNAs H19, GASS, TUG1 and CBR3-AS1 showed a significant upregulation in the luminal subtype (p < 0.05) whereas SNHG16 showed an exclusive suppression. MALAT1 was suppressed in the basal subtype. A distinct cutoff of the lncRNA H19 allowed a risk stratification into high- and low-risk pa- tients. The luminal subtype and H19 were the only independent risk factors in multivariate analysis adjusted for TNM and were predictive for a 3- to 4-fold higher risk of death (p < 0.03).

Conclusions: In this study, MIBC subtypes have been validated by a sensitive quantifi- cation method. Molecular subtypes and H19 prove to be independent risk factors su- perior to TNM. This study demonstrates for the first time a differential expression of lncRNA between MIBC subtypes. The potential impact of lncRNA on phenotype deter- mination has to be investigated in vivo.

Legal entity responsible for the study: IRIDGE Consortium

Funding: None

Disclosure: R. Sébastien: Novartis Research Fund. All other authors have declared no conflicts of interest.
**Table: 865P Results of the Cox analyses for the OS endpoint**

<table>
<thead>
<tr>
<th>Univariate comparison (N = 1,544):</th>
<th>Covariate</th>
<th>HR Lower 0.95</th>
<th>Upper 0.95</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Group: ACT vs. No ACT</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Matched analysis (N = 570):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group: ACT vs. No ACT</td>
<td>1.14</td>
<td>0.90</td>
<td>1.43</td>
<td>0.268</td>
</tr>
<tr>
<td>Propensity score-adjusted comparison (ATE approach, N = 1,544):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group: ACT vs. No ACT</td>
<td>1.31</td>
<td>1.08</td>
<td>1.58</td>
<td>0.005</td>
</tr>
<tr>
<td>Doubly-robust procedure (ATE approach, N = 1,544):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group: ACT vs. No ACT</td>
<td>1.26</td>
<td>1.02</td>
<td>1.54</td>
<td>0.032</td>
</tr>
<tr>
<td>Age: ≥61</td>
<td>1.33</td>
<td>1.18</td>
<td>1.49</td>
<td></td>
</tr>
<tr>
<td>ECOG-PS: 1 vs. 0.2 vs. 0</td>
<td>1.37</td>
<td>1.18</td>
<td>1.58</td>
<td>0.001</td>
</tr>
<tr>
<td>Pathologic stage: pT3-4N0 vs. pT2N0</td>
<td>1.30</td>
<td>0.92</td>
<td>1.72</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Abbreviations:** ACT: adjuvant chemotherapy; ATE: average treatment effect; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; HR: hazard ratio; OS: overall survival.

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**865P Impact of cisplatin-based therapy on long-term survival in advanced urinary tract cancer (aUTC). A retrospective international study of invasive/advanced cancer of the urothelium (RISC)**

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1Clinical Therapeutics, National and Kapodistrian University of Athens, Athens, Greece, 2Department of Urology, Evangelismos Hospital, National and Kapodistrian University of Athens, Athens, Greece, 3Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, 4Medical Oncology, Southampton General Hospital Southampton University Hospitals NHS Trust, Southampton, UK, 5Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA, 6Medical Oncology, City of Hope, Duarte, CA, USA, 7Medical Oncology, Istituto Tumori della Regina Margherita I.R.S.T., Meldola, Italy, 8Medical Oncology, Centre Georges-Francois Leclerc, Dijon, France, 9Medical Oncology, Huntsman Cancer Institute, Salt Lake City, UT, USA, 10Medicine, University of Washington, Seattle, WA, USA, 11Department of Urology, Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany, 12Department of Oncology, San Camillo and Forlanini Hospitals, Rome, Italy, 13Medical Oncology, Stanford University, Stanford, CA, USA, 14Solid Tumor Oncology, Wayne State University, Karmanos Cancer Center, Detroit, MI, USA, 15Medical Oncology, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, 16Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA, 17Barts Cancer Institute, Queen Mary University of London, London, UK, 18Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, 19Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA

**Background:** Cisplatin-based chemotherapy is the treatment of choice in aUTC. Nevertheless, about 30% of patients are unfit for this treatment. Long-term survival of patients with aUTC has not been adequately studied outside the context of clinical trials. In addition, the impact of cisplatin utilization on long-term survival has not been adequately addressed. We used a multinational database to study long-term survival and the impact of treatment type in unslected aUTC patients as well as to provide benchmarks for future trials.

**Methods:** Selection criteria: Diagnosis of aUTC, non small-cell histologies, administration of 1st-line chemotherapy, survival data available. Major end point: Overall survival (OS). Fitness-for-cisplatin (FFC) was defined according to Galsky et al (2011). Landmark and conditional survival analysis was used to study the change of prognosis with time from initiation of 1st-line chemotherapy.

**Results:** 1361 patients (median fup: 31 months) were analysed. Survival analyses are shown in the table.

Cisplatin therapy and FFC were associated with improved long-term survival. FFC patients have a 28% probability of 5-year survival, which is increased to 74% for the 34% of patients who survive 3-years after initiation of cisplatin-based chemotherapy.

**Conclusions:** Published criteria for FFC accurately predict for long-term survival of aUTC patients, following cisplatin-based chemotherapy, while patients not treated with cisplatin have inferior outcome. Probability of long-term survival was increased with time after initiation of 1st-line (cisplatin or no-cisplatin) therapy.

**Legal entity responsible for the study:** RISC investigators

**Funding:** None

**Disclosure:** Y-N. Wong: The author was at Fox Chase Cancer Center at the time the study was conducted but is now a Janssen Scientific Affairs employee. All other authors have declared no conflicts of interest.

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**Table: 865P**

<table>
<thead>
<tr>
<th>Probability of surviving (y) (%)</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received Cisplatin (n = 689) Did not receive cisplatin (n = 672)</td>
<td>28 13</td>
<td>23 10</td>
<td>19 6</td>
</tr>
<tr>
<td>FFC (n = 421) Unfit (n = 550)</td>
<td>28 13</td>
<td>22 10</td>
<td>18 8</td>
</tr>
<tr>
<td>Received Cisplatin/Fit (n = 295) Did not receive cisplatin/unfit (n = 368)</td>
<td>34 11</td>
<td>28 10</td>
<td>28 6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Probability of surviving 2 more years having lived (y) (observed/predicted) (%)</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received Cisplatin Did not receive cisplatin</td>
<td>44/43 30/52</td>
<td>54/62 48/47</td>
<td>62/67 43/57</td>
</tr>
<tr>
<td>FFC Unfit</td>
<td>45/43 31/52</td>
<td>64/60 56/53</td>
<td>64/69 61/66</td>
</tr>
<tr>
<td>Received Cisplatin/Fit Did not receive cisplatin/unfit</td>
<td>49/49 29/52</td>
<td>67/65 57/55</td>
<td>82/74 58/68</td>
</tr>
</tbody>
</table>
Correlation of circulating tumor DNA (ctDNA) profile in metastatic urothelial carcinoma (mUC)

1Medical Oncology, Dana Farber Cancer Institute, Boston, MA, USA, 2R & D, Foundation Medicine, Cambridge, MA, USA, 3Medical Oncology, Cleveland Clinic, Cleveland, OH, USA, 4Pathology, Foundation Medicine, Cambridge, MA, USA, 5Medical Oncology, City of Hope, Duarte, CA, USA

Background: Tissue-based CGP reveals a multitude of actionable targets in patients (pts) with mUC (Ross et al Cancer 2015). Assessment of ctDNA from blood offers the benefit of avoiding risks of biopsy/surgery and allows for serial assessment.

Methods: In pts with mUC, 30-100 ng of ctDNA was extracted from plasma during routine clinical care. Using adapted sequencing libraries, hybrid capture and sample multiplexed sequencing was performed with an Illumina HiSeq 2500 platform to a median coverage depth of 655X. This CLIA-certified test of 62 genes detected genomic alterations (GAs) at low allele frequencies (0.1% for substitutions, 1% for indels), rearrangements and 28% for copy number amplification. In several pts CGP data was available from separate tissue-based CLIA-certified tests for which methods have been previously reported (Frampton et al Nat Biotechnol 2013). In addition to examining intra-patient differences, we compared the cumulative frequency of GAs in ctDNA to a large pool of tissue-based CGP in mUC (n = 2024).

Results: 27 pts (18.9 M:F) with mUC had ctDNA assay; median age 68 (range, 52-86). There was evidence for ctDNA in the blood for 25/27 pts (93%), and at least 1 GA was observed in 20/27 (74%) cases. The most frequently altered genes were TP53 (63%), TERT (27%), FGFR3 (19%), PIK3CA (15%), BRCA2 (11%), NRAS (11%), EGFR (11%), and ERBB2 (9%). With the caveat of a limited sample size, the cumulative frequency of selected clinically relevant GAs was distinct in ctDNA and tissue. The frequency of FGFR3 alterations (in ctDNA as compared to tissue) was 7% vs 11% (P = 0.28) for BRCA2 (9% vs 11%), NF1 (6% vs 8%) (P = 0.56). In a pt with BRCA2 and TP53 GAs in baseline tumor tissue, ctDNA collected at the time of resistance to cisplatin-based therapy showed persistence of ERBB2 and TP53 GAs and a new NFI GA.

Conclusions: Using hybrid capture-based genomic profiling of ctDNA, ctDNA was detected in the vast majority of pts with mUC. Utility was demonstrated through detection of potential resistance mutations in pts receiving chemotherapy and targeted agents.

Legal entity responsible for the study: Siraj Ali

Funding: None


Comparison of circulating tumor DNA (ctDNA) profile in metastatic urothelial carcinoma (mUC) derived from the upper tract (UT) and lower tract (LT)

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Background: We have previously reported ctDNA profile in 246 patients (pts) with mUC derived from the UT (mUTUC) (Grivas et al ASCO GU 2017). mUC was derived from the UT (mUTUC) is a distinct entity with a more aggressive disease course. The ctDNA profile of mUTUC has not been previously characterized.

Methods: Data was obtained from pts with mUTUC who received ctDNA profiling as a part of routine clinical care using a CLIA-certified, CAP-accredited platform evaluating up to 70 genes. Genomic alterations (GAs) were pooled for the entire cohort. Comparison to the previously reported mUTUC was performed using the chi-square test.

Results: Between Oct 2014 and Apr 2017, ctDNA results from 75 pts (M:F 30:45) with mUC were assessed. Median age of the cohort was 69 (range, 40-90). A median of 6.2 months had elapsed from the time of diagnosis with mUC and ctDNA assay. Genomic alterations (GAs) were detected in 71 pts (95%), with an average/median of 4.53 GAs per pt (range, 0-35). Treatment related data was available in 30 pts (40%). The frequency of GAs in mUTUC vs mLTUC was as follows: TP53 (51% vs 52%), PIK3CA (20% vs 18%), ARID1A (16% vs 17%), EGFR (8% vs 13%), ERBB2 (8% vs 9%), FGFR3 (7% vs 11%), NRAS (6% vs 7%), BRAF (6% vs 8%) and NFI (6% vs 8%) (P = NS for all comparisons). Alteration types were diverse; for instance, FGFR3 alterations included fused (17%), TGCA (5%), and mutation (5294C; n = 3) and Y637C (n = 2). Correlation of ctDNA profile with treatment and clinical outcome will be presented at the meeting.

Conclusions: Despite representing a clinically distinct entity, mUTUC demonstrated a ctDNA profile similar to that of mLTUC. These data may inform the design of clinical trials of targeted therapy (e.g., FGFR3 and ERBB2 inhibitors) in mUC, suggesting that inclusion of both mUTUC and mLTUC may be warranted.

Legal entity responsible for the study: Neeraj Agarwal

Funding: None


Expression of Galectin-1 Determines Tumor Recurrence and Cancer-Specific Survival in Patients with pT3 Upper Urinary Tract Urothelial Carcinoma

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1Department of Urology, Chang Gung Memorial Hospital-Kaohsiung, Kaohsiung, Taiwan, 2Radiation Oncology, Chang Gung Memorial Hospital-Kaohsiung, Kaohsiung, Taiwan

Background: Upper urinary tract urothelial carcinoma (UTUC) is an aggressive and lethal disease. For patients with locally advanced UTUC, recurrence of tumor is frequent, and lacks of predictive biologic markers limited the choice of postoperative treatment. Galectin-1 (GAL1) is a β-galactoside-binding protein, participating in many parts of tumorigenesis, including cell proliferation, invasiveness, metastasis, and angiogenesis. However, the role of GAL1 in UTUC has not been fully investigated. The aim of this study was to examine the prognostic impact of GAL1 in patients with UTUC.
Results: Transcriptional subtypes were robustly assigned to 24/25 pts: 13 were classified as CL, 8 as B, and 3 as L. Basic clinicopathologic characteristics were comparable between two groups. In univariate analysis, high GAL1 expression was significantly associated with a worse recurrence-free survival (RFS) (p = 0.028) and cancer-specific survival (CSS) (p = 0.025). Multivariate analysis showed GAL1-high is an independent factor for RFS (HR 2.45, 95% CI 1.17-5.05, p = 0.018) and CSS (HR 4.04, 95% CI 1.25-13.05, p = 0.030). In vitro study, we found that knockdown of GAL1 reduced UTUC cancer cell migration and invasion significantly.

Conclusions: Galectin-1 expression is a reliable prognostic factor for locally advanced UTUC. GAL1 inhibition may serve as a potential therapeutic target for patients with UTUC.

Legal entity responsible for the study: Yu-Li Su

Funding: None

Disclosure: All authors have declared no conflicts of interest.

**RFS (HR 2.45; 95% CI 1.17-5.05, p = 0.019). In vitro study, we found that knockdown of GAL1 reduced UTUC cancer cell migration and invasion significantly.**

**Methods:** The study enrolled 86 UTUC patients who underwent radical nephroureterectomy and bladder cuff excision with full pathologically diagnosed as pT3N0 stage between January 2005 and December 2012. Perioperative characteristics and pathologic features were collected. Immunohistochemical staining of tumor specimens using anti-GAL1 antibody were performed. UTUC cell line (BFTC-909) was used for in vitro study of tumor invasiveness and migration. Kaplan-Meier analyses and Cox proportional regression models were used for univariate and multivariate survival analyses.

**Results:** Using 10% expression of GAL1 protein as a cut-off point, the study population could be classified as GAL1-high (GAL1 > 10%), n = 35) or GAL1-low (GAL1 ≤ 10%; n = 51) group. Basic clinicopathologic characteristics were comparable between two groups. In univariate analysis, high GAL1 expression was significantly associated with a worse recurrence-free survival (RFS) (p = 0.028) and cancer-specific survival (CSS) (p = 0.025). Multivariate analysis showed GAL1-high is an independent factor for RFS (HR 2.45; 95% CI 1.17-5.05, p = 0.018) and CSS (HR 4.04; 95% CI 1.25-13.05, p = 0.030). In vitro study, we found that knockdown of GAL1 reduced UTUC cancer cell migration and invasion significantly.

**Conclusions:** Galectin-1 expression is a reliable prognostic factor for locally advanced UTUC. GAL1 inhibition may serve as a potential therapeutic target for patients with UTUC.

Legal entity responsible for the study: Yu-Li Su

Funding: None

Disclosure: All authors have declared no conflicts of interest.

**871P Identification of genomic features underlying response of muscle-invasive bladder cancer (MIBC) to neoadjuvant sorafenib, gemcitabine, and cisplatin (SGC) in an open-label, single-arm, phase 2 study**

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**Background:** Genomic analyses demonstrated that MIBC can be grouped into molecular subtypes that portend different outcomes with neoadjuvant chemotherapy (NACT). SGC was active in MIBC, showing a response rate (downstaging to pT < 2) of 34.3% in 46 patients (pts) in a phase 2 trial (NCT01222876, Necchi et al. GUSC 2017). We analyzed gene expression profiles (GEP) and copy number variations (CNV) of transurethral resections (TURB) from these pts.

**Methods:** We analyzed 25 pts, 18 responders (R) and 7 non-responders (NR). GEP and CNV profiles were generated using Affymetrix Clarion™ and OncoScan™ assays. Samples were assigned to claudin-low (CL), basal (B) or luminal (L) subtypes according to the BASE47 and BCL40 signatures. Genes differentially expressed or amplified/deleted between NR and R were functionally analyzed using Ingenuity Pathway Analysis (IPA) and Gene Set Enrichment Analysis.

**Results:** Transcriptional subtypes were robustly assigned to 24/25 pts: 13 were classified as L, 10 CL and 1 B. A significant association between subtypes and therapeutic response was observed (p = 0.002), with all L samples falling in the R group while CL were split between R and NR (5 vs 5). To avoid confounding related to the subtype we restricted the comparison of R and NR to CL samples. Through the use of IPA we identified activation of an IRF7-driven transcriptional program (p = 3.88E-12) in NR samples. In the IRF7 pathway, we identified enrichment of genes involved in TLR signaling, cell cycle and oxidative phosphorylation and a negative enrichment of defensins. In addition, 19 genes were both significantly overexpressed and amplified in NR whereas copy number gains on chromosome 17, 18 and 20 characterized R samples. Limitations include the unassessable role of S contribution to GC.

**Conclusions:** Altogether, the results indicate that L tumors are responsive to SGC. Comparisons between R and NR within the CL group outlined potential genomic predictors of response. Once validated, pt selection criteria for NACT may be substantially improved. Comparison with profiling of response to NA pembrolizumab will be shown (NCT02736266).

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale dei Tumori

Funding: Affymetrix

Disclosure: All authors have declared no conflicts of interest.

**Table 872P Outcomes based on plasma biomarkers in METEOR, a randomized phase 3 trial of cabozantinib (c) vs everolimus (e) in advanced renal cell carcinoma (RCC)**

<table>
<thead>
<tr>
<th>Plasma Biomarker</th>
<th>C vs E, Hazard Ratio (95% CI) for OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Biomarker</strong></td>
<td><strong>High Biomarker</strong></td>
</tr>
<tr>
<td>HGF</td>
<td>0.48 (0.32, 0.70)</td>
</tr>
<tr>
<td>MET</td>
<td>0.67 (0.48, 0.94)</td>
</tr>
<tr>
<td>Gas6</td>
<td>0.53 (0.37, 0.75)</td>
</tr>
<tr>
<td>AXL</td>
<td>0.54 (0.38, 0.76)</td>
</tr>
<tr>
<td>VEGF</td>
<td>0.51 (0.36, 0.74)</td>
</tr>
<tr>
<td>VEGFR2</td>
<td>0.63 (0.46, 0.86)</td>
</tr>
<tr>
<td>IL-8</td>
<td>0.62 (0.43, 0.88)</td>
</tr>
</tbody>
</table>

**Conclusions:** PFS and OS improved with C irrespective of baseline plasma biomarker levels in previously treated pts with advanced RCC vs E. However, low baseline levels of a subset of biomarkers were associated with better clinical outcomes with C.

**Clinical trial identification:** NCT01865747

Legal entity responsible for the study: Exelixis, Inc.

Funding: Exelixis, Inc.

Ongoing: Results from Stage 1 of the phase 2a will be presented.

Methods: This Phase 2a study with a 2-stage design (NCT02030067) evaluates the efficacy of RX-3117 in eligible subjects (aged ≥ 18 years) with advanced urothelial cancer previously treated with an unlimited number of prior therapies. Primary objectives include safety and efficacy of the recommended Phase 2 dose (RP2D) and schedule identified in the Phase 1 portion of the study. Subjects received 700 mg of oral RX-3117 daily for 3 weeks with 1 week of rest in each 4-week cycle. The response criteria of complete and partial responses (RECIST v1.1) were used for more subjects or stable disease for 4 cycles in 2 or more subjects in Stage 1 in order to proceed to Stage 2.

Results: As of May 2017, 10 subjects with advanced urothelial cancer were treated with RX-3117 (4 females, 6 males). Of those 10 subjects, 78% received ≥ 3 prior therapies, had performance score of 0-1 and multiple disease sites (lung, liver, lymph nodes and pelvis). Two subjects met the protocol defined response criteria of 1 or more subjects or stable disease for 4 cycles in 2 or more subjects in Stage 1 in order to proceed to Stage 2.

Conclusion: Single agent RX-3117 appears to be safe and well tolerated and shows evidence of preliminary tumor activity. The predefined efficacy criteria was met in Stage 1, and Stage 2 is ongoing. Results from Stage 1 of the phase 2a will be presented.

Clinical trial identification: NCT02030067
Legal entity responsible for the study: Rexahn Pharmaceuticals, Inc
Funding: Rexahn Pharmaceuticals, Inc

875P Outcomes of patients with metastatic urothelial carcinoma (mUC) with exclusive bone metastases: Focus on a special patient population.


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Background: Patients (pts) with aUC with exclusive bone metastasis represent a rare subgroup of pts with unique clinical features. These pts deserve special consideration, as they are usually excluded from clinical trials due to the lack of measurable disease according to RECIST criteria. We focused on their access to treatment and outcomes in a retrospective study.

Methods: Cases were extracted from the pool of 1,911 pts with a diagnosis of mUC from the RISC database (db). Data from 23 centers was collected. Results of 1st-line, platinum-based chemotherapy in bone-only pts were compared with those from the remaining pts in the RISC db. Summary statistics were used to describe pt characteristics and stage. Kaplan-Meier method was used to estimate time to event outcomes such as progression-free survival (PFS) and overall survival (OS). Both OS and PFS are measured from the date of diagnosis of metastatic disease. Univariable and multivariable Cox analyses were performed. All tests were two-sided and statistical significance was defined as a p-value <0.05.

Results: A total of 128 evaluable pts (67.6%), treated between 02/1997 and 04/2013, were identified. ECOG-PS was ≥1 in 85.9% and 66.3% of the remaining pts from the RISC db. 37 (57%) received 1st-line chemotherapy, that was platinum-based in all pts, and 28 of them (38.4%) 2nd-line CT (vs. 75.8% and 42.5%, respectively, from the RISC db). On multivariable analyses, only the chemotherapy administration was significantly associated with improved OS among bone-only mUC pts (p < 0.001). Among platinum-treated pts (total evaluable N = 972), significantly different PFS and OS estimates were observed according to the bone metastases status (no bone metastases vs. bone metastases only vs. bone + other, p < 0.001). 2-year PFS was 37.4%, 28.8%, 25.9%. 2-year OS was 65.5%, 54.5%, 23.6%, among the above subgroups, respectively.

Conclusions: Pts with bone only metastases in mUC have a worse systemic therapy than pts with metastases to other sites, likely due to lower PS. The prognostic impact of having exclusive bone metastases or additional sites seems to be equally poor. Clinical trials with new agents should focus on this population.
**Efficacy of cabozantinib (C) after PD-1/PD-L1 checkpoint inhibitors in metastatic renal cell carcinoma (mRCC): The Gustave Roussy experience**

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**Background:** Optimal treatment sequence in mRCC remains unclear, although PD-1/PD-L1 inhibitors are becoming standard of care in second or third-line. There is little evidence about the efficacy of antiangiogenic therapies after immune checkpoint inhibitors (ICI), especially of C, which was recently approved for mRCC. We report our initial experience of C efficacy after prior ICI.

**Methods:** We conducted a retrospective analysis of mRCC patients (pts) enrolled on clinical trials at Gustave Roussy with ICI with a special focus on C as subsequent therapy. Clinical outcome during C treatment, including Time to Treatment Failure (TTF), Objective Response Rate (ORR), Overall Survival (OS) and safety are reported.

**Results:** After a median follow-up of 60 months (mo), among 127 pts treated with ICI (n: 107, nivolumab), 44 (35%) were still on-treatment and 5 pts had stable disease after treatment interruption. Among the 79 pts who progressed, and after ICI, 22 pts (28%) never received further treatment. 56 pts (72%) received further therapies: 18 (32%) C, 25 (44%) Axitinib (A) and 13 (24%) other (O). C was given as third-line or beyond in 27% and 73% of pts, respectively. Before starting C pts were only intermediate or poor prognosis by IMDC criteria. Considering all evaluable pts, ORR was 33%, median TTF was 7.99 mo and median OS was 12.33 mo. Focusing on C, ORR was 42% and no pts presented progressive disease as best response versus 37% for A with 2% progressive disease. Currently, median TTF and OS on C are not yet estimable (0.92 not reached), update on clinical outcome will be presented. Moreover, C demonstrated acceptable safety profile and the rate of treatment discontinuation because of adverse events was 11%.

**Conclusions:** In mRCC pts previously treated by ICI, treatment with C seems to be very active, irrespective of number of prior treatments or IMDC risk group. Prior PD-1/PD-L1 exposure did not influence safety of subsequent C therapy. Interestingly, activity of a of also appears excellent, raising the hypothesis of enhanced efficacy of TKI after ICI.

**Legal entity responsible for the study:** Not applicable

**Funding:** None

**Disclosure:** All authors have declared no conflicts of interest.

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**Comparing ITC results from lenvatinib plus everolimus for second-line treatment of advanced/metastatic renal cell carcinoma: Crossover versus no crossover**

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**Background:** An indirect treatment comparison (ITC) involving lenvatinib plus everolimus (LEN + EVE) was conducted using networked data from HOPE 205, CHECKMATE-025, METEOR, AXIS, RECORD-1 and TARGET. The ITC incorporated adjustments for crossover to investigational treatment. Results showed superiority of LEN + EVE over EVE alone; and inferiority versus pazopanib (PAZ) or sunitinib (SUN) alone in overall survival (OS) for second-line treatment of advanced/metastatic renal cell carcinoma. No statistically significant differences in OS were found between LEN + EVE versus nivolumab (NIV), cabozantinib (CAB), axitinib (AXI), or placebo.

**Methods:** A subsequent analysis was conducted using intention to treat (ITT) to evaluate the impact of crossover correction on OS estimates and additionally to uncover any potential bias due to its absence. Three ITC scenarios were analyzed: A) all comparators plus placebo versus EVE; B) all comparators versus placebo; and C) LEN + EVE versus all comparators.

**Results:** Scenario “A” showed consistent variance in survival benefit for ITT versus crossover by an average of 20%. Hazard ratios for AXI versus EVE shifted from below null (0.98) to above null (1.27); and mortality risk (placebo vs. EVE) moved 51% further from null (1.15 vs. 1.67). ITT estimates for Scenarios “B” and “C” showed on average 9% and 14% differences in OS estimates, respectively, versus crossover. In Scenario “C”, estimates for LEN + EVE versus PAZ or LEN + EVE versus SUN showed superiority with ITT data (0.82 vs. 0.75) but were inferior (1.2 or 1.09) with crossover.

**Conclusions:** Bias was observed in naive approaches to survival analysis in the presence of crossover. Failure to account for this in clinical trials may have implications on the comparative effectiveness profile and also on the cost-effectiveness results, may lead to inconsistent resource allocation decisions.

**Legal entity responsible for the study:** Eisai Inc

**Funding:** Eisai Inc

**Disclosure:** G. Meier, M. Guo. Employees of Eisai Inc. H. McElroy: Employee of Covance Market Access Services, which was paid by Eisai for literature review and statistical analysis. All other authors have declared no conflicts of interest.

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**Second-line treatment patterns and outcomes of metastatic bladder cancer patients in clinical practice**

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**Background:** There is no universally accepted standard therapy for second-line (2L) treatment of metastatic bladder cancer (mBC). We sought to evaluate treatment patterns and outcomes of patients (pts) receiving 2L treatment for mBC.

**Results:** Of 1155 pts receiving 1L treatment during the index period, 391 (33.9%) pts who subsequently received 2L therapy were included in this analysis. The Kaplan-Meier estimated median time-to-event for all 2L regimens was 5.2 mos (95% confidence interval [CI], 4.5 to 6.0). For the composite outcome of third-line therapy initiation or death, the median time-to-event for all 2L regimens was 5.2 mos (95% confidence interval [CI], 4.5 to 6.0).

**5% of total 2L utilization)**

**Conclusions:** In mBC pts previously treated by ICI, treatment with C seems to be very active, irrespective of number of prior treatments or IMDC risk group. Prior PD-1/PD-L1 exposure did not influence safety of subsequent C therapy. Interestingly, activity of a of also appears excellent, raising the hypothesis of enhanced efficacy of TKI after ICI.

**Legal entity responsible for the study:** Not applicable

**Funding:** None

**Disclosure:** All authors have declared no conflicts of interest.

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**Urine-derived lymphocytes (UDLs) as a non-invasive surrogate marker of tumour infiltrating lymphocytes (TILs) in patients with muscle invasive bladder cancer (MIBC)**

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**Background:** The therapeutic targeting of PD-1 and PD-L1 has led to durable responses in metastatic bladder cancer, yet the majority of patients (pts) fail to respond. Here, we characterised the immune phenotype and TCR repertoire in tumour and UDLs in patients with MIBC for the identification of potential('') T cell biomarkers of response and resistance to checkpoint blockade.

**Methods:** Matched bladder tumour, normal urethra (NU), urine and peripheral blood mononuclear cells (PBMC) were collected from 30 pts undergoing cystectomy. Multi-parametric flow cytometry and immunohistochemistry were used to determine the abundance of CD8(+) TILs (CD8(+)FoxP3(+) and CD8(+)FoxP3(-) (Treg) T cell subsets and co-inhibitory (PD-1, CTLA-4, TIM-3) and co-stimulatory (ICOS, 4-1BB) immune response and resistance to checkpoint blockade.

**Results:** Scenario “A” showed consistent variance in survival benefit for ITT versus crossover by an average of 20%. Hazard ratios for AXI versus EVE shifted from below null (0.98) to above null (1.27); and mortality risk (placebo vs. EVE) moved 51% further from null (1.15 vs. 1.67). ITT estimates for Scenarios “B” and “C” showed on average 9% and 14% differences in OS estimates, respectively, versus crossover. In Scenario “C”, estimates for LEN + EVE versus PAZ or LEN + EVE versus SUN showed superiority with ITT data (0.82 vs. 0.75) but were inferior (1.2 or 1.09) with crossover.

**Conclusions:** Bias was observed in naive approaches to survival analysis in the presence of crossover. Failure to account for this in clinical trials may have implications on the comparative effectiveness profile and also on the cost-effectiveness results, may lead to inconsistent resource allocation decisions.

**Legal entity responsible for the study:** Eisai Inc

**Funding:** Eisai Inc

**Disclosure:** G. Meier, M. Guo. Employees of Eisai Inc. H. McElroy: Employee of Covance Market Access Services, which was paid by Eisai for literature review and statistical analysis. All other authors have declared no conflicts of interest.
checkpoint molecules. T cell receptor (TCR) repertoire was determined using quantitative high throughput sequencing of α and β TCR chains followed by Decombinator bioinformatics analysis.

Results: UDLs were identified in 19/24 (80%) of MBc pts with tumour in situ compared to 6/9 (66.7%) pts with pathological downstaging (pT0) following neo-adjuvant therapy. Urea, tumour and PBMC specimens were found to have a similar CD8/Treg ratio that was significantly higher in NU. Co-stimulatory and co-inhibitory checkpoint molecules were similarly distributed across CD8+ CD69 and Treg within tumour, urine and NU compartments, however significantly different to PBMC irrespective of prior treatment. Preliminary analysis revealed a higher degree of similarity between the TCR repertoires of urinary matched tumour as compared with urine and NU or urine and PBMC samples.

Conclusions: These data suggest that UDLs are an accessible source of T cells from pts with MBc that accurately map the immune landscape of TILs. UDL analysis represents a liquid biopsy to inform clinically relevant immunological parameters, including the CD8/Treg ratio, target checkpoint expression and TCR repertoire, irrespective of prior treatment. Further translational studies are ongoing to evaluate whether UDL analysis may serve as a non-invasive, dynamic biomarker to predict immunotherapy outcome in MBc.

Clinical trial identification: University College London (UCL)/University College London Hospital (UCLH) Biobank for Health and Human Disease (NC06.11)

Legal entity responsible for the study: UCL/UCLH

Funding: UCL/UCLH

Disclosure: C. Swanton: Grants/research supports: Pfizer Honoraria or consultation fees: Roche Ventana, Celgene, Pfizer, Novartis; Stock shareholder: Grail, Epic Biosciences, Apteon Biotechnologies, Achilles Therapeutics. T. Powles: Research fund-fees: Roche Ventana, Celgene, Pfizer, Novartis; Stock shareholder: Grail, Epic Biosciences, Apteon Biotechnologies, Achilles Therapeutics. A. Mejean: Fees from Pfizer, Novartis, Bristol-Myers Squib, Ipsen, A. Thiery-Vuillemin: Grants and personal fees from Pfizer and personal fees from Novartis, Bristol-Myers Squib, Ipsen, personal fees from Roche; grants from JNJ, N. Mottet: Fees from Sanofi, Astellas, Janssen. B. Escudier: Honorarium received from: Bristol-Myers Squib, Novartis, Pfizer, Ipsen, Roche, Bayer, Calithera, Acceleron, EURO, Eisai. L. Albige: Fees from Pfizer, Novartis, Bristol-Myers Squib, Ipsen, Bayer, Merck. All other authors have declared no conflicts of interest.

## 881P

**Biomarkers before and after nephrectomy of locally advanced or metastatic renal cell carcinoma (RCC) treated with everolimus: Neoad: Phase 2 trial (PREDICT consortium)**


Background: Although many drugs are available in RCC, we still lack predictive biomarkers of disease recurrence or progression for personalized treatment. NEORAD clinical trial (NCT01715955) was designed to evaluate biomarkers modulation by everolimus (Ev) prior to nephrectomy on several tissue and circulating cells.

Methods: French open-label, exploratory, single-arm, multicenter trial, part of PREDICT consortium. Population: locally-advanced (LA), metastatic (M) RCC. Endpoints: primary: objective clinical benefit (CR, PR, SD upon RECIST 1.1) after 6 weeks neoadjuvant Ev (10 mg daily) prior nephrectomy; secondary: PFS, OS, toxicity. Multi-region sequencing (biopsy and surgery specimens) explored mutualistic status of genes of interest. After nephrectomy, Ev was reintroduced in M pts until PD or end of 12m follow-up. Treatment was continued until PD or unacceptable toxicity.

Results: 25 pts accrued (44 screened) between 05/2012 and 07/2015: LA = 14, M = 11 underwent biopsy at screening for tissue sampling then further nephrectomy. Population (LAMV): clear-cell=13/19, papillary=1/1, median age(y): 60/63, sarcoma-toid-component: 3 M pts, ECOG-PS: 0=10/14, 1=4/7, extra-renal metastatic sites: bone, lung, nodes, adrenal. Change in renal tumor size between baseline and D42: 0%. In M, Ev was resumed for 8 pts after nephrectomy with 2 PR and 6 SD. PFS (mos): M = 3.1 [1.41;12.2]. Median follow-up (mos): 17.4 [3.4;43.2]. PFS at 12 months: LA = 78%, M = 18%. Toxicity of Ev was as expected and no adverse event in terms of surgical procedure was observed. Pts with following gene mutations exhibited a poor PFS: SEDT2: HR = 2.54 (0.63 – 10.28), BAP1: HR = 3.19 (1.08 – 13.12), TSC2: HR = 2.37 (0.49 –11.53); further correlations will be presented at ESMO meeting.

Conclusions: NEORAD was the 1st neoadjuvant study of Ev in RCC. Despite limited number of pts, we generated a large amount of longitudinal data including genome sequencing, circulating biomarkers, angiogenesis and immunity factors. All these data could help decipher mechanisms of resistance, evaluate predictive signatures or add further knowledge to mechanisms in mTOR pathways.

Clinical trial identification: NCT01715955

Legal entity responsible for the study: Stéphane Oudard, MD, PhD

Funding: PREDICT Consortium

Disclosure: S. Oudard: Grants and personal fees from Pfizer, personal fees from Novartis, Bristol-Myers Squib, Ipsen, Bayer, outside the submitted work. A. Mejean, J.J. Patard: Fees from Pfizer, Novartis, Bristol-Myers Squib, Ipsen. A. Thiery-Vuillemin: Grants and personal fees from Pfizer, during the conduct of the study; grants and personal fees from Pfizer, Bristol-Myers Squib, Ipsen; personal fees from Roche; grants from JNJ, N. Mottet: Fees from Sanofi, Astellas, Janssen. B. Escudier: Honorarium received from: Bristol-Myers Squib, Novartis, Pfizer, Ipsen, Roche, Bayer, Calithera, Acceleron, EUSA, Eisai. L. Albige: Fees from Pfizer, Novartis, Bristol-Myers Squib, Ipsen, Bayer, Merck. All other authors have declared no conflicts of interest.

## 881P

**Predicted benefits of adjuvant sorafenib after nephrectomy for renal cell carcinoma (RCC) in SORCE: an international, placebo-controlled, randomised phase 3 trial**

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Background: The effects on survival of adjuvant therapy with a VEGF-TKI after nephrectomy for RCC are uncertain. Survival rates, times and benefits were predicted by medical oncologists at baseline for each patient they recruited to SORCE.

Methods: Medical oncologists at 20 sites in ANZ and 12 in the UK answered the following questions at baseline for each patient they recruited: the predicted overall survival rate at 5 years (SR) and predicted overall survival time (ST) without adjuvant sorafenib; and, the predicted absolute improvements in SR and ST with 1 year of adjuvant sorafenib. We used Spearman’s rank correlation (rS) to assess associations, and Wilcoxon signed rank tests to assess differences between the paired SR–ST values. We assumed exponential survival distributions to calculate: (i) % alive at 5-yrs corresponding to SR estimates, and (ii) hazard ratios (HRs) corresponding to predicted benefits on overall survival. We hypothesized that these HRs should be less extreme (numerically larger) than the target HR of 0.75 for disease free survival used to design the trial.

Table: 881P

<table>
<thead>
<tr>
<th></th>
<th>ST1 In Years</th>
<th>ST1 Calculated % alive at 5-yrs [a]</th>
<th>SR1 Estimated % alive at 5-yrs [b]</th>
<th>Difference1</th>
<th>rS</th>
<th>[a] vs [b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival without sorafenib</td>
<td>7 (5 to 12)</td>
<td>61 (50 to 75)</td>
<td>60 (50 to 70)</td>
<td>0 (-7 to 9)</td>
<td>0.62</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Improvement with sorafenib</td>
<td>1 (1 to 5)</td>
<td>6 (3 to 10)</td>
<td>7 (5 to 15)</td>
<td>-2 (-5 to 1)</td>
<td>0.53</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.83 (0.67 to 0.91)</td>
<td>0.83 (0.67 to 0.91)</td>
<td>0.76 (0.62 to 0.82)</td>
<td>0.09 (-0.01 to 0.21)</td>
<td>0.41</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Medians (IQRs)</td>
<td></td>
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Results: The table shows paired estimates of ST and SR from 61 medical oncologists for 176 of the 1711 SOCRE patients. Predictions of survival without sorafenib were similar whether based on ST or SR. The predicted benefits of sorafenib based on SR were moderately correlated with those based on ST, but significantly larger. The proportion of HRs > 0.75 was 51% based on SRs vs 66% based on STs.

Conclusions: The predicted benefits of adjuvant sorafenib based on SRs were often larger than hypothesized, and larger than predictions based on ST, which were more consistent with the target HR. These data suggest that predictions of benefit in this setting may be more conservative and plausible when based on ST rather than SR.

Clinical trial identification: NCT00492258

Legal entity responsible for the study: NHMRC Clinical Trials Unit, University of Sydney

Funding: Cancer Australia, NHMRC, Bayer, CRUK


882P Potential impact of avelumab + axitinib (A+Ax) on tumor size (TS) compared with historical data of sunitinib (S) as evaluated by a modeling and simulation (MS) approach

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1Pharmacometrics, Global Product Development, Pfizer Inc., Collegeville, PA, USA, 2Clinical Pharmacology, Pfizer Inc., San Diego, CA, USA, 3Medical Oncology, Longsword Hospital NIVS Foundation Trust, London, UK, 4Medical Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA, 5Pharmacometrics, Pfizer Inc., San Diego, CA, USA, 6Medical Oncology, Pfizer Inc., New York, NY, USA, 7Biostatistics, Pfizer Inc., New York, NY, USA, 8Immuno-Oncology, Pfizer Inc., Milan, Italy, 9Immuno-Oncology, Pfizer Inc., San Diego, CA, USA

Background: Combining an immune checkpoint inhibitor (Ax) with a targeted antiangiogenic agent (S) may leverage complementary mechanisms of action for treatment of metastatic renal cell carcinoma (mRCC). JAVELIN Renal 100 is a phase III study of Avelumab + Axitinib (A+Ax) vs S in the JAVELIN 101 randomized Ph3 trial. References: 1. Motzer R et al. (2017). J. Clin. Oncol. 35, 7085-7093. 2. JAVELIN Renal 100 Ph3 trial. 3. LCSM-5437-304-001 (2017). JAVELIN Renal 101 randomized Ph3 trial. The model includes 5 parameters representing the rate of tumor growth (KL), the rate of drug effect in reducing tumor size (KD), and the rate of the loss of drug effect (DM). The TR8 for each patient can be derived from the model. A larger KD, smaller DM, and TR8 suggests a greater effect. The parameters and TR8 from the two treatments are estimated and compared using ANOVA.

Methods: A tumor dynamic model was applied to the longitudinal TS data obtained from the Ph Ib study of A+Ax and from the historical Ph3 trial of S. The model includes 5 parameters representing the rate of tumor growth (KL), the rate of drug effect in reducing tumor size (KD), and the rate of the loss of drug effect (DM). The TR8 for each patient can be derived from the model. A larger KD, smaller DM, and TR8 suggests a greater effect. The parameters and TR8 from the two treatments are estimated and compared using ANOVA.

Results: The summaries of the model parameters, TR8, and p-value of ANOVA analysis are presented in the Table below.

Table: 882P

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Median (± SE)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>TR8</td>
<td>Time to response</td>
<td>0.757 ± 0.162</td>
<td>0.808 ± 0.132</td>
</tr>
<tr>
<td>KL (1/week)</td>
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<td>0.011 ± 0.014</td>
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<tr>
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A+Ax resulted in a greater effect on TR8, a faster tumor size reduction and a more sustained effect than S.

Conclusions: MS is an effective tool to inform drug development. These results suggest that A+Ax results in a greater TS reduction than S, supporting further investigation of A+Ax vs S in the JAVELIN 101 randomized Ph3 trial. References: 1. Motzer R et al. (2017). J. Clin. Oncol. 35, 7085-7093. 2. JAVELIN Renal 101 Ph3 trial. 3. LCSM-5437-304-001 (2017). JAVELIN Renal 101 randomized Ph3 trial. The model includes 5 parameters representing the rate of tumor growth (KL), the rate of drug effect in reducing tumor size (KD), and the rate of the loss of drug effect (DM). The TR8 for each patient can be derived from the model. A larger KD, smaller DM, and TR8 suggests a greater effect. The parameters and TR8 from the two treatments are estimated and compared using ANOVA.

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Background: Ineligibility for clinical trials (CT) may be an unfavorable prognostic factor in mRC. There is no information about the effectiveness of pazopanib in patients (pt) ineligible for CT. We aimed to assess the effect of ineligibility in outcomes in mRC, and the effectiveness of pazopanib in this setting.

Methods: SPAZO2 (NCT03091465) was a retrospective real-world study to analyze the effectiveness of 1st-line pazopanib and subsequent therapies in mRC in several settings. Data from 530 pt treated with frontline pazopanib outside CT in 50 centers in Spain were collected, and externally monitored. Ineligibility criteria: ELOG ≥ 1, pure non-clear-cell, brain metastases, Hgb < 9 g/dl, renal failure, severe ischemic disease, age > 80 y, stroke, chronic liver disease, or recent neoplasia.

Results: A total of 217 pt (40.9%) fulfilled criteria for ineligibility. There were significant differences (I vs E) in age (> 75 (99% vs 75%), nephrectomy (61% vs 78%), IMDC (favorable: 8.8 vs 17.9%, intermediate: 30.2% vs 68.4%, poor: 41% vs 13.2%), metastases (lymph nodes: 51% vs 41%, lung: 65% vs 72%, liver: 21% vs 15%, bone: 31% vs 22%, skin/soft-tissue: 30% vs 16%, and CNS (13% vs 0%) but not in sex (68% vs 67% males). Discontinuation due to toxicity or comorbidities was 19% vs 17%. There were also differences (p < 0.05) in 2nd-lines (53% vs 61%), response, PFS and OS (Table). Median follow-up was 39 mo. Median PFS and OS were 9.8 and 19.6 mo respectively. After adjusting by IMDC and age (Cox regression), ineligibility was significantly associated with a higher risk of progression (HR: 1.49 95%CI: 1.1 - 1.7) and death (HR: 1.59 95%CI: 1.2 - 1.9). Only anemia and asthenia (all grades) were significantly higher in the I group.

Conclusions: In our series, “real world eligible pt” had similar outcome to the obtained in clinical trials. On the contrary, “real world ineligible pt” for clinical trials had significantly lower response rate, and shorter PFS and OS than eligible pt. Pazopanib was safe and effective in both subpopulations of patients.

Clinical trial identification: NCT03091465

Legal entity responsible for the study: SOGUG

Funding: Novartis

Disclosure: J Arranz Arija: Grant for research from Novartis. Participation in advisory boards for Novartis and Pfizer. B. Pérez Valderrama: Consulting/Advisory role for Astellas Pharma, Novartis, Pfizer, Pierre Fabre, Bayer, Sanofi, Bristol-Myers Squib and Roche. J.P. Maroto Rey: Advisory Board for Novartis, Pfizer, Ibsen and Bristol. M.A. Climent Duran: Pfizer and Novartis talks, advisory role for Pfizer. All other authors have declared no conflicts of interest.

Table: 884P Association of time to metastases with OS and TTF from TKI initiation

<table>
<thead>
<tr>
<th>time to metastases</th>
<th>Total</th>
<th>Failed</th>
<th>Median, months 95% CI</th>
<th>Adjusted Hazard ratio (95% CI)</th>
<th>Adjusted P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3mo</td>
<td>3906(53%)</td>
<td>2852</td>
<td>16.7(15.9-17.5)</td>
<td>1.00 (reference)</td>
<td>−</td>
</tr>
<tr>
<td>&gt;3-12mo</td>
<td>1055(14%)</td>
<td>726</td>
<td>23.8(21.6-26.1)</td>
<td>1.06(0.98-1.16)</td>
<td>0.162</td>
</tr>
<tr>
<td>&gt;1-2yrs</td>
<td>638%(98%)</td>
<td>401</td>
<td>30.0(26.3-32.5)</td>
<td>0.84(0.76-0.94)</td>
<td>0.002</td>
</tr>
<tr>
<td>&gt;2-7yrs</td>
<td>1155(16%)</td>
<td>729</td>
<td>34.8(32.4-34.8)</td>
<td>0.76(0.70-0.83)</td>
<td>&lt;0.001 1151 1011 7.3(6.6-8.0) 1.02(0.95-1.10) 0.551</td>
</tr>
<tr>
<td>&gt;7yrs</td>
<td>632%(99%)</td>
<td>359</td>
<td>41.7(36.3-46.0)</td>
<td>0.65(0.58-0.73)</td>
<td>&lt;0.001 627 527 13.0(15.1-19.9) 0.67(0.61-0.74) &lt;0.001</td>
</tr>
<tr>
<td>Total</td>
<td>7386(100%)</td>
<td>5676</td>
<td>43.6(39.5-47.9)</td>
<td>0.59(0.55-0.63)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Table: 883P Association of time to metastases with OS and TTF from TKI initiation

<table>
<thead>
<tr>
<th>OS</th>
<th>MedianOS</th>
<th>Adjusted Hazard ratio (95% CI)</th>
<th>Adjusted P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Failed</td>
<td>Median, months 95% CI</td>
</tr>
<tr>
<td></td>
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<td>3906(53%)</td>
<td>2852</td>
</tr>
<tr>
<td></td>
<td>&gt;3-12mo</td>
<td>1055(14%)</td>
<td>726</td>
</tr>
<tr>
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<td></td>
<td>Total</td>
<td>7386(100%)</td>
<td>5676</td>
</tr>
</tbody>
</table>

Table: 884P

<table>
<thead>
<tr>
<th>Overall</th>
<th>N = 530</th>
<th>N = 217</th>
<th>N = 313</th>
<th>Favourable (14.2%)</th>
<th>IMDC prognostic subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>E</td>
<td>I</td>
<td>E</td>
<td>I</td>
</tr>
<tr>
<td>CR</td>
<td>4.4%</td>
<td>1%</td>
<td>7%</td>
<td>5%</td>
<td>11%</td>
</tr>
<tr>
<td>PR</td>
<td>28.5%</td>
<td>23%</td>
<td>33%</td>
<td>42%</td>
<td>52%</td>
</tr>
<tr>
<td>SD</td>
<td>37.3%</td>
<td>42%</td>
<td>34%</td>
<td>32%</td>
<td>33%</td>
</tr>
<tr>
<td>Median PFS*</td>
<td>9.8</td>
<td>7.7</td>
<td>11.5</td>
<td>13.5</td>
<td>23.5</td>
</tr>
<tr>
<td>Median OS*</td>
<td>19.6</td>
<td>12.8</td>
<td>24.4</td>
<td>29</td>
<td>42.3</td>
</tr>
</tbody>
</table>

*Months (IC95%); I: ineligible; E: eligible.
Sunitinib versus pazopanib for patients with metastatic renal cell carcinoma: a retrospective comparative case series study

M. Dervis1, E. Aydin1, I. Cift2, A. Zirhiloglu1, D. Tural1, S. Karabulut2
1Medical Oncology, Istanbul University Institute of Oncology, Istanbul, Turkey, 2Medical Oncology, University of Health Sciences, Bakirkoy Dr Sadi Konuk Education and Research Hospital, Istanbul, Turkey

Background: Pazopanib (PAZ) and Sunitinib (SUN), are two oral multikinase angiogenesis inhibitors which are prescribed frequently. However, the outcomes in real world of Turkish population have not been extensively studied.

Methods: Patients assessed retrospectively at two Turkish hospitals between 2006 and 2016.

Results: Median age of patients was 60 (28-87) years and 70% of patients were male. ECOG performance score was 0 and 1 in 73% of patients. Twelve patients (15%) had non-clear cell carcinoma histology. Pathological characteristics, MSKCC risk groups, median follow-up, response rates and survival are shown in Table. In the SUN group, the patients had more grade 3-4 adverse events (Table).

Table: 885P Patient characteristics, responses to treatment, survival, and adverse events

<table>
<thead>
<tr>
<th>MSKCC risk group</th>
<th>Sunitinib (n = 41)</th>
<th>Pazopanib (n = 38)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>31%</td>
<td>31%</td>
<td>0.66</td>
</tr>
<tr>
<td>Intermediate</td>
<td>56% Poor</td>
<td>47% Poor</td>
<td>0.21</td>
</tr>
<tr>
<td>12.5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3-T4 stage</td>
<td>49%</td>
<td>47%</td>
<td>0.34</td>
</tr>
<tr>
<td>Node positivity</td>
<td>20%</td>
<td>8%</td>
<td>0.03</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>20%</td>
<td>30%</td>
<td>0.34</td>
</tr>
<tr>
<td>Median follow-up</td>
<td>18 months</td>
<td>13 months</td>
<td>0.21</td>
</tr>
<tr>
<td>ORR</td>
<td>34%</td>
<td>50%</td>
<td>0.04</td>
</tr>
<tr>
<td>DCR</td>
<td>78%</td>
<td>87%</td>
<td>0.06</td>
</tr>
<tr>
<td>Progression</td>
<td>73% (n = 30)</td>
<td>50% (n = 19)</td>
<td>0.08</td>
</tr>
<tr>
<td>Median PFS</td>
<td>8 months</td>
<td>8 months</td>
<td>0.49</td>
</tr>
<tr>
<td>Median OS</td>
<td>22 months</td>
<td>21 months</td>
<td>0.21</td>
</tr>
<tr>
<td>Fatigue, all grades</td>
<td>45%</td>
<td>74%</td>
<td>0.04</td>
</tr>
<tr>
<td>Skin changes, all grades</td>
<td>44%</td>
<td>44%</td>
<td>0.42</td>
</tr>
<tr>
<td>Anemia, all grades</td>
<td>33%</td>
<td>42%</td>
<td>0.75</td>
</tr>
<tr>
<td>Grade 3-4 adverse events</td>
<td>59%</td>
<td>16%</td>
<td>0.001</td>
</tr>
<tr>
<td>Dose reduction</td>
<td>50%</td>
<td>24%</td>
<td>0.02</td>
</tr>
<tr>
<td>Treatment cessation</td>
<td>37%</td>
<td>26%</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Conclusions: In our study, there was no difference in terms of survival between two agents. However, patients treated with SUN had more grade 3-4 adverse effects which prompted dose reduction and cessation.

Legal entity responsible for the study: Individuals, Meltem Ekenel and Semen Karabulut

Funding: None

Disclosure: All authors have declared no conflicts of interest.

SPAZ02 (SOUG): Comparative effectiveness of everolimus (Ev) vs axitinib (Ax) as second-line after first-line pazopanib (1stPz) in metastatic renal carcinoma (mRC)

1Medical Oncology, Hospital General Universitario Gregorio Maranon, Madrid, Spain, 2Medical Oncology, Hospital Universitario de Leon, Leon, Spain, 3Medical Oncology, Hospital Universitario Río Hortega, Valladolid, Spain, 4Medical Oncology, Hospital Universitario La Paz, Madrid, Spain, 5Medical Oncology, Hospital Universitario Puerta de Hierro, Majadahonda, Spain, 6Medical Oncology, Hospital General Ciudad Real, Ciudad Real, Spain, 7Medical Oncology, Hospital Universitario Rio Hortega, Valladolid, Spain, 8Medical Oncology, Hospital Nuestra Senora de Valme, Seville, Spain, 9Medical Oncology, Hospital Sabadell Corporaco Parc Tauli, Sabadell, Spain, 10Medical Oncology, Hospital Clinico Universitario San Carlos, Madrid, Spain, 11Medical Oncology, Hospital Central de la Defensa Gomez Ulla, Madrid, Spain, 12Medical Oncology, Hospital Clinico Universitario Lazano Blesa, Zaragoza, Spain, 13Medical Oncology, Hospital Provincial de Pontevedra, Pontevedra, Spain, 14Medical Oncology, University Hospital Rena Sofia, Cordoba, Spain, 15Medical Oncology, Hospital Universitario Virgen Macarena, Seville, Spain, 16Medical Oncology, Hospital General Universitario de Elche, Elche, Spain, 17Medical Oncology, Catalan Institute of Oncology (ICO) Badalona, Hospital Girona Tris in Puig, Badalona, Spain, 18Medical Oncology, Hospital de Basurto, Bilbao, Spain, 19Medical Oncology, University General Hospital, Guadalajara, Spain, 20Medical Oncology, Hospital Clinico San Cecilio, Granada, Spain

Background: Pivotal studies of axitinib and everolimus in 2nd-line mRC did not indicate pt treated with 1stPz. In addition, Ev and Ax have not been directly compared in clinical trials in this setting. We aimed to compare the effectiveness of Ev vs Ax in real-life, as second-line after pazopanib in mRC.

Methods: SPAZ02 (NCT03091465) was a retrospective real-world study to analyze the effectiveness of 1stPz and subsequent therapies in mRC in several settings in every day practice. Data from 330 pt treated with frontline pazopanib outside CT in 50 centers in Spain were collected by investigators, but monitored and entered in a database by an external CRO. Result: Out of 285 pt receiving 2nd-line targeted therapies after 1stPz, 189 received either Ax (88, 46.6%) or Ev (101, 53.4%). There were no significant differences (Ax vs Ev), in age (63 y vs 66 y), sex (68% vs 64% males), nephrectomy (76% vs 67%), metastases in lymph nodes (58% vs 52%), liver (21% vs 28%), bone (45% vs 41%), CNS (6%), adrenal (4% vs 5%), pleural/peritoneum (4% vs 6%), or pancreas (4% vs 6%), but there were in age >75 (14% vs 25%), nonclear cell component (11% vs 16%), and lung (85 vs 72%) and skin/soft-tissue (20 vs 28%) metastases. According to the IMDC for 2nd-line targeted therapies, 17% vs 9% of pt were in the favorable risk group, 65% vs 69% in the intermediate risk, and 18% vs 22% in the poor risk. All-grades hypertension (32.6% vs 3.6%) and hypothyroidism (16% vs 6%) were significantly higher with Ax, whereas anemia (21.4% vs 55%), and mucositis (12.3% vs 39%) were more frequent with Ev. Subsequent therapies were given in 56% in Ax vs 46% in Ev. After median follow-up of 28 mo, 74.6 of pt have died. Outcomes and 95%CI are summarized in the table.

Table: 886P

<table>
<thead>
<tr>
<th></th>
<th>Response</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ORR</td>
<td>SD</td>
<td>Median</td>
</tr>
<tr>
<td>Axitinib</td>
<td>13.1%</td>
<td>42.9%</td>
<td>5.3 (3-7)</td>
</tr>
<tr>
<td>Everolimus</td>
<td>9.3%</td>
<td>43%</td>
<td>4.6 (3-6)</td>
</tr>
<tr>
<td>Overall</td>
<td>11.2%</td>
<td>42.9%</td>
<td>5.0 (4-6)</td>
</tr>
</tbody>
</table>

*Adjusted by IMDC, metastases, age, histology and subsequent therapies.

Conclusions: In this real world study in pt with mRC, we could not find statistically significant differences in effectiveness between axitinib and everolimus as 2nd-line after 1st-line pazopanib. These results validate the use of both drugs in terms of clinical benefit, PFS and OS.

Clinical trial identification: NCT03091465

Legal entity responsible for the study: SOUG

Funding: Novartis

Disclosure: J. Aranza Arja: AdBo from Novartis and Pfizer. B. Perez-Valderama: Consulting/Advisory role for Astellas Pharma, Novartis, Pfizer, Pierre Fabre, Bayer, Sanofi, Bristol-Myers Squib and Roche. J. Puertas Alvarez: Participation in advisory board meetings from Pfizer, Astellas, Novartis, Sanofi, GlaxoSmithKline, AstraZeneca, Pharmamar, Hospira, Janssen, Eisai, Roche, Lilly, and Bayer. All other authors have declared no conflicts of interest.
Background: In recent years, prognostic classifications have been considered an area of growing interest in mRCC. However, independently from the classification used (Memorial Sloan Kettering versus Heng’s) the presence of brain, liver and bone metastases is associated with worse outcomes.

Methods: Nivolumab was available upon physician request for pts aged > 18 years who relapsed after at least one prior systemic treatment in the advanced or metastatic setting. Nivolumab 3 mg/kg was administered intravenously every 2 weeks for a maximum of 24 months. Pts included in the analysis had received ≥ 1 dose of nivolumab and were monitored for adverse events (AEs) using Common Terminology Criteria for Adverse Events (CTCAE). Median NLR was 3.7 (1.3-16.1) at baseline and 3.9 (1.1-49.6) at week 6. Higher NLR at baseline and at 6-weeks showed a trend to reduced ORR and worse PFS and OS, and a decrease in NLR by ≥ 25% was associated with improved outcomes.

Conclusions: Early decline and NLR at 6-weeks are associated with significantly improved outcomes in mRCC patients treated with IO, whereas an increase is associated with worse outcomes.

---

Table: 888P

<table>
<thead>
<tr>
<th>N</th>
<th>ORR(CR+PR)</th>
<th>PFS</th>
<th>OS</th>
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<tr>
<td></td>
<td>Adjusted-OR</td>
<td>p-value</td>
<td>Adjusted-HR</td>
</tr>
<tr>
<td>Continuous Ln(NLR) Baseline**</td>
<td>116</td>
<td>0.58 (0.23-1.42)</td>
<td>0.232</td>
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<tr>
<td>Continuous Ln(NLR) 6-weeks**</td>
<td>113</td>
<td>0.28 (0.11-0.69)</td>
<td>0.006</td>
</tr>
<tr>
<td>NLR-change 6-weeks</td>
<td></td>
<td></td>
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<tr>
<td>Decrease ≥25%</td>
<td>22</td>
<td>1.63 (0.47-5.60)</td>
<td>0.67 (0.31-1.46)</td>
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<tr>
<td>No change</td>
<td>55</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
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<tr>
<td>Increase ≥25%</td>
<td>36</td>
<td>0.61 (0.22-1.66)</td>
<td>2.30 (1.30-4.07)</td>
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</table>

**Natural log-transformed

---

Table: 887P

<table>
<thead>
<tr>
<th>ECOG PS %</th>
<th>Age, median (range) (Male %)</th>
<th>Brain Mets (65 (43-77) 72)</th>
<th>Liver Mets 65 (43-81)</th>
<th>Bone Mets 65 (40-84)</th>
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</thead>
<tbody>
<tr>
<td>0 1 2 NA</td>
<td>41 50 6 3</td>
<td>42 50 7 1</td>
<td>39 48 10 3</td>
<td></td>
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<tr>
<td>1 2 3 &gt;= 4 NA</td>
<td>13 44 36 0</td>
<td>13 37 24 2</td>
<td>14 36 30 19 1</td>
<td></td>
</tr>
</tbody>
</table>

---

887P Negative prognostic factors and resulting clinical outcome in patients (pts) with metastatic renal cell carcinoma (mRCC) included in the Italian nivolumab expanded access program (EAP)

S. Bracarda¹, L. Galli¹, M. Maruzzi², G. Lo Re³, S. Buñ³, A. Favaretto³, F.D. Costanzo³, C. Sacco³, M. Melefrano³, C. Mucciarini³, E. Zafatana³, S. Romito³, A. Maestrì³, C. Carminotto Giorgio⁴, M.T. Ionta⁵, D. Tuco⁶, U. De Giorgi⁷, G. Procopio⁸, E. Cortelli⁹, C. Porta¹⁰

¹Oncology, Ospedale San Donato USL,Sud-Est, IT; ²Az. L. Dino, Milan, Italy; ³Oncology, Azienda Ospedaliero Universitaria Pisana Istituto Toscana Tumori, Pisa, Italy; ⁴Oncology, Istituto Oncologico Veneto IRCCS, Padua, Italy; ⁵CRO Aviano, Ospedale Pordenone-S. Vito, CRO Aviano, Pordenone, Italy; ⁶Medical Oncology, Azienda Ospedaliero Universitaria Parma, Parma, Italy; ⁷Specialized Medicine Department, Oncology Unit, AUSL 2, Treviso Hospital, Treviso, Italy; ⁸Oncology, ASLU Careggi, Florence, Italy; ⁹Oncology, ASLUD, Udine, Italy; ¹⁰Clinical Oncology, Azienda Ospedaliero Universita' di Cagliari, Cagliari, Italy.

Results: Of 389 Italian pts with mRCC enrolled in the EAP, 32 pts (8%) had brain mets, 93 pts (24%) had liver mets and 193 (50%) had bone mets. Baseline characteristic are described in Table. These pts achieved a disease control rate (DCR) of 53%, 45% and 47% respectively. Six and 12 months OS rate of 61% and 53.6% for the 3 groups of mets were 87.0%, 86.5% and 86.0%, 75.6% and 62.0%, 78.0% and 58.9%, respectively. Histological grading, a surrogate of prognosis, was 25% at 6-weeks was associated with improved outcomes.

Conclusions: These results suggest that also pts with poor prognostic factors may derive relevant benefits with nivolumab, with safety results consistent with previously reported data.

Clinical trial identification: Expanded Access Program

Legal entity responsible for the study: Italian RCC EAP Group

Funding: None

Disclosure: S. Bracarda: Advisory Board Member for Pfizer, Novartis, Bristol-Myers Squib, Exelixis, Ipsen, Roche, Genentech, Eusa Pharma. PI for clinical studies with Bristol-Myers Squib, Pfizer, Roche, Exelixis. L. Galli: Advisory Board for Pfizer, Novartis. U. De Giorgi: Advisory Board for Bristol-Myers Squib, Pfizer, Novartis, Ipsen, Astellas, Janssen, Sanofi. G. Procopio, C. Porta: Advisory Board for Bristol-Myers Squib, Pfizer, Novartis, Ipsen. E. Cortelli: Advisory Board for Bristol-Myers Squib, Pfizer, Ipsen. All other authors have declared no conflicts of interest.

888P Change in neutrophil-to-lymphocyte ratio (NLR) in response to immunotherapy for metastatic renal cell carcinoma (mRCC)

A.K. Lalani², W. Xié², D. Martínez², C.K. Norton³, J.A. Steenbergen³, D. Bossé³, J. Bellmunt⁴, E.M. Van Allen⁵, I.A. McGregor⁵, L.C. Harshman⁵, T.X. Chuen⁵, L. van der Kwast⁵

¹Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; ²Dept. of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA, USA

Background: Elevated NLR is associated with worse outcomes in several malignancies, including mRCC. However, its role in the current immunotherapy era is unknown. We investigated the utility of NLR at baseline and during therapy in mRCC patients treated with PD-1/PD-L1 immunotherapy (IO).

Methods: 116 patients from Dana-Farber Cancer Institute (Boston, MA) receiving IO-based therapies were included. NLR was examined at baseline and 6 (±2) weeks later. Landmark analysis at 6 weeks was conducted to explore the prognostic value of relative NLR change on overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) using Cox or logistic regression models, adjusted for line of therapy, number of IMDC risk factors, histology and baseline NLR.

Results: Median follow up was 16.3 months (range: 1-46.4). Median duration on therapy was 7 months (1-58.6). IMDC risk groups were: 21% favorable, 56% intermediate, 22% poor-risk. 43% were on first-line IO and 57% on 2nd line or more. Median NLR was 3.7 (3.1-16.1) at baseline and 3.9 (1.1-49.6) at 6 weeks. Higher NLR at baseline and at 6 weeks showed a trend to reduced ORR and worse PFS and OS, and NLR at 6-weeks was a stronger prognostic than baseline values (Table). Compared with no change from baseline, increase in NLR by ≥ 25% at 6-weeks was associated with reduced ORR and significantly worse PFS and OS in multivariate analysis, whereas a decrease in NLR by ≥ 25% was associated with improved outcomes.

Conclusions: Early decline and NLR at 6-weeks are associated with significantly improved outcomes in mRCC patients treated with IO, whereas an increase is associated...
with worse outcomes. The prognostic value of the readily-available NLR warrants larger, prospective validation.

Legal entity responsible for the study: Dana-Farber/Harvard Cancer Center

Funding: None

Disclosure: J. Bellmunt: Research support from Novartis and Sanofi; consulting sup-
port from OncoGeneX, AstraZeneca, Merck, Bristol Myers-Squibb, Genentech, Inc., and
Champions Oncology, Seattle Genetics and Pierre Fabre. E.M. Van Allen: Stock and
Other Ownership Interests: Synaps; Consulting or Advisory Role: Novartis, Roche,
Synapse, Takeda, Third Rock Ventures; Research Funding: Bristol-Myers Squibb T.K.
Chauvet: Consulting: Bayer, Bristol-Myers Squibb, GlaxoSmithKline, Merck, Nu-
ovartis, Pfizer, Research Funding: AstraZeneca, Bristol-Myers Squibb, Exelixis,
GlaxoSmithKline, Merck, Novartis, Peloton Therapeutics, Pfizer, Roche/Genentech,
TRACON Pharma. All other authors have declared no conflicts of interest.
Conclusions: In this small retrospective study, we observed a high response rate (41%), median PFS 10 months, and manageable toxicity in patients with mRCC treated with TKI after ICI. No patients had outright PD on 2L TKI after ICI.

Legal entity responsible for the study: MD Anderson Cancer Center Dept of Genitourinary Medical Oncology

Funding: None


Disclosure: All authors have declared no conflicts of interest.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total n (%)</th>
<th>PR (n)</th>
<th>SD (n)</th>
<th>P value</th>
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<tr>
<td>Male</td>
<td>19 (70)</td>
<td>7</td>
<td>12</td>
<td>0.68</td>
</tr>
<tr>
<td>Female</td>
<td>8 (30)</td>
<td>4</td>
<td>4</td>
<td></td>
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<tr>
<td>Localized at presentation</td>
<td>9 (33)</td>
<td>7</td>
<td>2</td>
<td>0.01</td>
</tr>
<tr>
<td>Metastatic at Presentation</td>
<td>18 (67)</td>
<td>14</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>IMDC good risk</td>
<td>4 (15)</td>
<td>3</td>
<td>1</td>
<td>0.47</td>
</tr>
<tr>
<td>IMDC intermediate risk</td>
<td>19 (70)</td>
<td>12</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>IMDC poor risk</td>
<td>4 (15)</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Nephrectomy</td>
<td>21 (78)</td>
<td>10</td>
<td>11</td>
<td>0.35</td>
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<tr>
<td>Primary in-situ</td>
<td>6 (22)</td>
<td>5</td>
<td>1</td>
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<tr>
<td>Pazopanib</td>
<td>8 (30)</td>
<td>4</td>
<td>4</td>
<td>0.37</td>
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<tr>
<td>Axitinib</td>
<td>12 (44)</td>
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<td>9</td>
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<tr>
<td>Cabozantinib</td>
<td>7 (26)</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: In this small retrospective study, we observed a high response rate (41%), median PFS 10 months, and manageable toxicity in patients with mRCC treated with TKI after ICI. No patients had outright PD on 2L TKI after ICI. Legal entity responsible for the study: MD Anderson Cancer Center Dept of Genitourinary Medical Oncology Funding: None Disclosure: G. Ianu: Travel/Honoraria & Consulting: AstraZeneca. M.T. Campbell: Consulting/advisory role: AstraZeneca. Jonasch: Research support: Exelixis, Pfizer, Novartis, Argos, Calithera Research: Bristol-Myers Squib, Exelixis. Prof. Enrico Cortesi: Travel/Honoraria & Consulting: Bristol-Myers Squib, Exelixis, Merck.

Disclosure: All authors have declared no conflicts of interest.
**Background:** Only 2% of pt included in the IMDC prognostic model for 2nd-line tar
targeted agents in mRC had received pazopanib (1stPz) in metastatic renal cell carcinoma (mRC).

**Methods:** SPAZ02 (NCT03914465) was a retrospective real-world study to analyze the ef
effectiveness of imatinib and subsequent therapies in mRC in several settings in every day practice.

**Results:** A total of 285 pt received antiVEGF or mTOR inhibitor as 2nd line (37.6% everolimus, 23.9% temsirolimus, 36% axitinib, 9.9% sunitinib, 8.3% sorafenib, 2.9% cabozantinib, 2.1% pazopanib, and 0.4% bevacizumab). 0% somatostatin, 2.1% pazopanib, 0.4% bevacizumab (136 metastases) were treated by Gamma Knife Surgery (GKS) and received a median dose on the 50% prescription isodose of 18 Gy (14-22). The minimal and maximal median dose was respectively 18.4 Gy (12.5-30) and 36 Gy (23.5-51.2). Sixty-three patients (36 metastases) were treated by linear accelerator photon 10 MV. The minimal (iso-
dose 70%) and maximal (isocentre) median dose were respectively 16 Gy (9.8-25.8) and 20.3 Gy (15.3-33.74). The median disease-free survival time is 5.5 months (0-252). The median survival time between the first brain metastasis diagnosis and death is 15.3 months (0.3-147). The tumor growth control rates at 3, 6, 12 months are respectively 86%, 62%, 36%. Following the 187 stereotactic irradiations, 95 (51%) cerebral disease progressions are recorded, after a median time of 5 months (1-81); 81 progressions (85%) are due to new lesions and 25 (26%) due to local failures. Analyses of prognostic factors related to survival are still in process.

**Conclusions:** Stereotactic radiosurgery is associated with a high local control of brain metastasis from RCC without whole brain radiotherapy. The two described modalities present different characteristics whose advantages will be further discussed with the as-

cessment of prognostic and predictive factors of local control.

**Legal entity responsible for the study:** Assistance Publique des Hôpitaux de Paris (APHP)

**Funding:** None

**Disclosure:** All authors have declared no conflicts of interest.

---

**Table: SPAZ02**

<table>
<thead>
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<th>Overall</th>
<th>FR</th>
<th>IR</th>
<th>PR</th>
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<tbody>
<tr>
<td>ORR</td>
<td>14.6%</td>
<td>22.5%</td>
<td>15.8%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Median PFS (1*)</td>
<td>5.1 (4-6)</td>
<td>11.5 (6-18)</td>
<td>5 (4-6)</td>
<td>3 (2-4)</td>
</tr>
<tr>
<td>Median PFS (2*)</td>
<td>4.7 (4-5)</td>
<td>9.7 (4-15)</td>
<td>4.8 (4-15)</td>
<td>3 (2-4)</td>
</tr>
<tr>
<td>Median OS (1*)</td>
<td>11.3 (9-13)</td>
<td>24.4 (18-30)</td>
<td>12.7 (10-15)</td>
<td>6.5 (5-8)</td>
</tr>
<tr>
<td>Median OS (2*)</td>
<td>11.1 (9-13)</td>
<td>19.8 (12-27)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Months: 1* - 2nd-line due to any cause (N = 285); 2* - 2nd-line due to progression to Pz (N = 242).
stable disease, and I had progressive disease. Median duration on treatment was 6.0 months (range 4.6-12.1).

Conclusions: The combination treatment of XP-001 and axitinib is well tolerated with preliminary evidence of clinical activity. The Ph2 portion of the study is ongoing.

Clinical trial identification: NCT02667886 First received: January 20, 2016

Legal entity responsible for the study: X4 Pharmaceuticals

Funding: X4 Pharmaceuticals


M.B. Atkins: Compensated consultant for Bristol-Myers Squibb, Merck, Roche, Pfizer, Novartis, Peletor, AstraZeneca, Nektar, Acceleron, Eisai and Exelixis and serve on Advisory Boards for X4 Pharma, Merck, Novartis, Roche, Pfizer, Galactose, Agenus and AVEO. All other authors have declared no conflicts of interest.

Efficacy and safety data in elderly patients (pts) with metastatic renal cell carcinoma (mRCC) included in the nivolumab expanded access program (EAP) in Italy


1Oncology, AOU Policlinico, Modena, Italy, 2Oncology, AOU Pisana Istituto Toscano A. Bonetti 15, L. Giustini 16, S. Duranti 17, G. Procopio 18, C. Caserta 19, G. Carteni 20

Oncologia Area Vasta 4, Fermo, Italy, 17Oncology, Azienda ASL8, Arezzo, Italy, 15Oncology, Ospedale Mater Salutis, Legnago, Italy, 16UOC, Medical Oncology, Hospital Clinic y Provincial de Barcelona, Barcelona, Spain, 14Oncology, Tumori, Pisa, Italy, 3IRCCS, Fondazione G. Pascale, Naples, Italy, 4AO, Santa Maria degli Angeli, Pordenone, Italy, 13Radiotherapy, AOU Careggi, Florence, Italy, 12UO, Oncology, A.O. A. Cardarelli, Napoli, Italy

Nivolumab 3 mg/kg was administered intravenously every 2 weeks to a maximum of nivolumab in this subpopulation. Nivolumab was available upon physician request for pts aged at least one comorbidity requiring treatment, leaving them exposed to drug interactions.

Methods: Adverse Events.

Background: The risk of developing renal cell carcinoma (RCC) increases with age, and given the constant gain in life expectancy of the general population, RCC is frequent in elderly patients. With a median follow-up of 9.8 months (0.1-75 years) in the EAP in Italy, given a more realistic picture of real world setting. The purpose of this analysis is to evaluate the feasibility of treatment with safety results consistent to what previously reported, supporting the use of nivolumab in this subpopulation.

Results: Of 389 Italian pts with mRCC enrolled in the EAP in Italy 125 pts (32%) had ≥70 years and 70 (18%) had ≥75 years. With a median follow-up of 9.8 months (0.1-16.2) in the elderly population (≥70 years), the disease control rate (DCR) was 58% including 1 patient in complete response (CR), 32 pts in partial response (PR) and 40 patients in stable disease (SD). Regarding the very elderly population (≥75 years), with a median follow-up of 9.8 months (0.1-14.9), the DCR was 60% including 1 patient with CR, 19 pts with PR and 22 with SD. As of May 2017, 6 and 12 months overall survival (OS) rate were 87.3% and 77.8% respectively in the elderly population. Regarding the very elderly, the 6 and 12 months OS rate was 83.6% and 77.7%, respectively. The safety profile was consistent to what already observed in the general population.

Conclusions: These results suggest that elderly population can benefit from nivolumab treatment with safety results consistent to what previously reported, supporting the use of nivolumab in this subpopulation.

Clinical trial identification: CA209-99M

Legal entity responsible for the study: Sergio Bracarda coordinator Italian RCC EAP Group

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Immune expression profile and sunnibin benefit in metastatic clear renal cell carcinoma (cRCC)

O. Berja Torres1, M. Marin-Aguilera1, J. Jimenez1, L. Pare1, P. Galvan1, C. Malafosse2, A. Prat1, B. Mellaerts Gonzalez5

1Medicall Oncology, Hospital Clinic y Provincial de Barcelona, Barcelona, Spain, 2Pathology, Hospital Clinic y Provincial de Barcelona, Barcelona, Spain

Background: The identification of predictive biomarkers may be useful to select antiangiogenic or immunotherapy treatment in renal cell carcinoma. We have investigated the immune expression profile in sunnibin (SU) or anti-PD1/PD-L1 treated ccRCC patients.

Methods: Forty-two metastatic ccRCC patients treated with SU and 10 patients treated with anti-PD1/PD-L1 antibodies were included in this retrospective biomarker study. 78 immune related genes (mCytOff-PanCancer Immune Profiling Panel, Nanostring) were tested in FFPE tumor specimens. Different immune gene signatures were correlated with clinical outcome. A differential expression analysis between refractory (progression-free survival (PFS) < 3 months) and sensitive (PFS > 3 months) patients to SU and anti-PD1/PD-L1 therapies was performed.

Results: Patients who achieved a partial or complete (CR/P) response with SU had a higher score of B cell, CD8 T cell, T cell, Th1 cell, Th2 cell, Treg cell and Stromal signatures. Moreover, these signatures were predictive of PFS to sunnibin (p-value for odds ratio < 0.05). T cell signatures (CD8 T cell, T cell, Th1 cell, Th2 cell and Treg cell) were correlated with a better PFS, whereas activated dendritic cell (aDC) and stromal signatures were correlated with a better OS (Table). In the cohort of anti-PD1/PD-L1 treated patients, no differences in the immune signatures were found between responders and non-responders to these drugs. However, differential expression analysis revealed a single gene, TIM-3, that was associated with resistance to anti-PD1/PD-L1 therapies and benefit to SU in ccRCC patients.

Conclusions: T cell signatures may be associated with benefit to SU in ccRCC. The value of TIM-3 as a potential biomarker in ccRCC merits further exploration.

Legal entity responsible for the study: Hospital Clinico de Barcelona

Funding: Fundación Clínico para la Recerca Biomédica

Disclosure: All authors have declared no conflicts of interest.
Methods: PAZOREAL is a prospective, non-interventional study to evaluate the effectiveness, tolerability, safety and quality of life of the routine tx of 450 adult patients (pts) with histologically confirmed mRCC treated with first-line PAZ, second-line EVE or NIVO, or third-line EVE after NIVO. The main objective is to assess efficacy of PAZ in the respective tx lines and overall, other objectives include overall survival, dosing parameters, safety and quality of life.

Results: Between December 2015 and March 2017, 305 pts have been enrolled; 302 in the third-line PAZ cohort and 3 in third-line EVE after NIVO. The latter cohort was opened for documentation after approval of NIVO. 266 first-line pts had a documented first intake of PAZ and were eligible for analysis; 201 (75.6%) had a clear-cell histology. Median TD on PAZ was 6.5 months. For 98 pts (36.8%) discontinuation of PAZ tx was reported. The main reasons were progressive disease (N = 36), followed by toxicity (N = 18) and (serious) adverse event (N = 13). Details on subsequent tx with NIVO or EVE were documented for 44 and 3 pts, respectively, while 6 pts started other therapies in second line and during PAZ tx, the most frequently reported treatment-emergent adverse events (TEAE) of grade 1/2 were diarrhea (N = 57), nausea (N = 36), and fatigue (N = 24), of grade 3/4 were hypertension (N = 11), diarrhea, and anemia (each N = 4). Fatal TEAEs were reported in 28 pts with progression being the most common term.

Conclusions: PAZ is an effective and safe first-line therapy for pts with mRCC in a real life setting. Second line therapy has rapidly shifted towards NIVO.

Clinical trial identification: BI4RM AWB No. 6687

Legal entity responsible for the study: Novartis Pharma GmbH

Funding: Novartis Pharma GmbH

Disclosure: I. Bedke: Reports consultancies, honoraria or study participation from Bayer, Bristol-Myers Squibb, Novartis, Pfizer and Roche. M. Wehlau: Reports grants from Novartis, during the conduct of the study. M. Schostak: Reports grants and other from Novartis, during the conduct of the study. C. van der Vlist: Grants from Novartis for scientific talks. C. Heringschubert: Reports grants from Roche, Novartis, Aimgen, Bristol-Myers Squib Böhringer and Cellgene, outside the submitted work. T. Wolf: Nothing to disclose. I. Schlüchter: Reports grants and personal fees from Bristol-Myers Squibb, Novartis; grants from Essai, Celgene; personal fees from Jansen, Pfizer, outside the submitted work. V. Grünwald: Advisory role at Pfizer, Novartis, Bristol-Myers Squibb, Ipsen, Essai, Roche and has received honoraria from Pfizer, Novartis, Bristol-Myers Squibb, Ipsen, Essai and Roche. Support is given from Pfizer, Novartis, Bristol-Myers Squibb and MSD Merck. R. Ehnes: Employee of Novartis Pharma GmbH and holds stocks or stock options of Novartis and of O&O. D. Klein: T. Medinger: Employed at oMEDICO AG. P.J. Goesb: Received honoraria for participation in expert rounds and honoraria/support as a speaker from Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Essai, Ipsen, Jansen, Novartis, Pfizer, Sanofi. All other authors have no conflicts of interest.

Table: 900P

<table>
<thead>
<tr>
<th>Dose level (n pts)</th>
<th>SU011248 (standard error)</th>
<th>SU012662 (standard error)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>During 1st course</td>
<td>During 1st course</td>
</tr>
<tr>
<td></td>
<td>mean change at optimal dose</td>
<td>mean change at optimal dose</td>
</tr>
<tr>
<td>50 mg (n = 27)</td>
<td>90.7 (5.2)</td>
<td>27.6 (2.6)</td>
</tr>
<tr>
<td>&lt; 50 mg (n = 13)</td>
<td>95.4 (10.1)</td>
<td>33.6 (4.6)</td>
</tr>
<tr>
<td>&gt;50 mg (n = 18)</td>
<td>77.1 (5.7)</td>
<td>21.4 (2.6)</td>
</tr>
<tr>
<td>After optimization</td>
<td>SU011248 (SE) at optimal dose</td>
<td>SU012662 (SE) at optimal dose</td>
</tr>
<tr>
<td>50 mg (n = 27)</td>
<td>78.9 (4.7)</td>
<td>27.5 (3.2)</td>
</tr>
<tr>
<td>&lt; 50 mg (n = 13)</td>
<td>72.8 (8.0)</td>
<td>21.7 (2.8)</td>
</tr>
<tr>
<td>&gt;50 mg (n = 18)</td>
<td>106.7 (11.9)</td>
<td>36.5 (3.6)</td>
</tr>
</tbody>
</table>

Conclusions: While dose individualization corrects for some of the differences in PK values on the 1st Rx course, differences remain even after dose optimization emphasizing the importance of pharmacodynamics for toxicity and outcome. An ongoing dose optimization may be important to correct for the decline in PK over time.

Clinical trial identification: NCT01499121

Legal entity responsible for the study: Dr. Geoff A Bjarnason and the Sunnybrook Research Institute

Funding: Pfizer Canada


901P

Safety and efficacy of Cabozantinib for metastatic renal cell carcinoma (mRCC): real world data from an Italian Expanded Access Program (EAP)


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Background: Higher SUN exposure is associated with better outcomes but SUN PK on day 28 does not correlate with toxicity (# 363, ASCO-GU 2012). The mean PK values declined over time in 27 pts that remained on 50 mg and a continued decline was seen in 61 pts with continued sampling. There was no significant difference in PKs at OS between dose levels for all 117 pts.

Results: Between December 2015 and March 2017, 305 pts have been enrolled; 302 in the third-line PAZ cohort and 3 in third-line EVE after NIVO. The latter cohort was opened for documentation after approval of NIVO. 266 first-line pts had a documented first intake of PAZ and were eligible for analysis; 201 (75.6%) had a clear-cell histology. Median TD on PAZ was 6.5 months. For 98 pts (36.8%) discontinuation of PAZ tx was reported. The main reasons were progressive disease (N = 36), followed by toxicity (N = 18) and (serious) adverse event (N = 13). Details on subsequent tx with NIVO or EVE were documented for 44 and 3 pts, respectively, while 6 pts started other therapies in second line and during PAZ tx, the most frequently reported treatment-emergent adverse events (TEAE) of grade 1/2 were diarrhea (N = 57), nausea (N = 36), and fatigue (N = 24), of grade 3/4 were hypertension (N = 11), diarrhea, and anemia (each N = 4). Fatal TEAEs were reported in 28 pts with progression being the most common term.

Conclusions: PAZ is an effective and safe first-line therapy for pts with mRCC in a real life setting. Second line therapy has rapidly shifted towards NIVO.
cell renal cell carcinoma who progressed after at least one previous antiangiogenic inhibitor. The EAP provided the opportunity to treat pts in real world clinical practice.

Methods: Data were collected from 91 pts treated with cabozantinib across 23 Italian hospitals. Cabozantinib was available, upon physician request, from September to December 2016. Pts were aged 18 years and older, with mRCC and measurable disease, with Performance Status (ECOG) 0 to 2, who had relapsed after one or more prior systemic treatment. 73 pts had clear-cell RCC, while the other 18 had non-clear-cell histologies (type II papillary and chromophobe). The most frequent sites of disease were: lung 53 (58%), lymph nodes 41 (45%), bone 28 (31%), liver 5 (5%) and brain 5 (5%) had two or more sites of disease. Cabozantinib was administered orally 40 mg once a day in 28 days-cycles. Dose reductions to 40 or 20 mg were allowed if toxicity was encountered. Pts were monitored for adverse events (AEs) using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v+4.0. The aim of this analysis was to evaluate the safety and activity of cabozantinib in a large unselected population.

Results: Cabozantinib was administered as second line therapy in 28 (30%) pts, as III line in 18 (19%) pts and as further lines in the remaining 45 (51%) pts. At the time of our analysis, 82 (90%) pts received cabozantinib 40 mg and 9 (10%) pts received 60 mg. At discontinuation treatment due to AEs. The best overall response was partial in 28 cases (31%), whereas 23 (25%) pts had stable disease and 23 (25%) pts had progressive disease; 17 pts (18%) had not reached the first response assessment. With a median follow-up of 4 months, the median progression-free survival observed was 3.3 months irrespective of the line of treatment.

Conclusions: Our data suggest that cabozantinib is safe and active in a large unselected population. Learn according to everyday clinical practice.

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale dei Tumori of Milan

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902P Prognostic factors for overall survival of patients with advanced renal cell carcinoma – data from the German prospective RCC-Registry

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Funding:
Disclosure:

Results: Biomarkers for outcome after immune-checkpoint blockade in mRCC are needed. We aimed to verify the prognostic impact of inflammatory indexes based on the Italian expanded access program (EAP)

904P Inflammatory indexes strongly predict clinical outcome in patients (pts) with metastatic renal cell cancer (mRCC) treated with nivolumab: results from the Italian expanded access program (EAP)

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Background: Biomarkers for outcome after immune-checkpoint blockade in mRCC are needed. We aimed to verify the prognostic impact of inflammatory indexes based on the Italian expanded access program (EAP).
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on baseline values of neutrophils (N), lymphocytes (L) and/or platelets (P) in pts with mRCC included in the Italian nivolumab EAP.

**Methods:** Pts who had received ≥ 1 dose of nivolumab 3 mg/kg every 2 weeks in the Italian EAP after at least one prior systemic therapy for mRCC were enrolled in this study. The pre-treatment systemic immune inflammation index (SII) defined as P/L ratio (PLR) defined as PL/L were evaluated to identify a potential correlation with overall survival (OS). A tile 5.1. software was used to identify cut-off values. OS was estimated by the Kaplan-Meier method and compared with the log-rank test. The impact of SII, NLR, and PLR on OS was evaluated by Cox regression analyses and on best overall response rate (ORR) by binary logistic regression.

**Results:** A total of 146 mRCC pts treated with nivolumab included. SII ≥ 1735, NLR ≥ 3 and PLR ≥ 232 were considered as elevated levels (high risk groups). One-year OS in low and high SII group was 77% and 36%, respectively (p < 0.0001); 1-year OS in low and high NLR was 76% and 58%, respectively (p < 0.0001); 1-year OS in low and high PLR was 76% and 45%, respectively (p < 0.0011). Likewise, best ORR was higher in pts with low SII (p = 0.008), low NLR (p = 0.06) and low PLR (p = 0.004). In multivariate analysis adjusted for age, gender, risk score (MDRCC), ECOG performance status, presence of liver, brain and/or bone mets, SII, NLR and PLR, the model identified SII as the strongest factor associated with OS (p < 0.0001).

**Conclusions:** SII, NLR, and PLR are robust inflammatory prognostic factors for predicting OS and OS with good accuracy. A more powerful predictive system than the other inflammatory indexes for these pts.

**Clinical trial identification:** expanded access program

**Legal entity responsible for the study:** Italian RCC EAP Group

**Funding:** None

**Disclosure:** U. De Giorgi: advisory board Bristol-Myers Squib. All other authors have declared no conflicts of interest.

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**906F Impact of haptoglobin polymorphism on survival of renal cell carcinoma patients**

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**Background:** Renal cell carcinoma (RCC) accounts for 2.4% of all malignancies worldwide with 338,000 estimated new cases globally in 2012. With 144,000 deaths annually, RCC is the 16th cancer-related death worldwide. In the last decade, the use of targeted therapy for patients with metastatic RCC has increased exponentially, especially since the breakthroughs with Sunitinib and nivolumab. Although from the Heng criteria in 1st-line therapy, no robust biochemical markers exist for the prognosis of RCC patients. Here we assessed the prognostic value of haptoglobin (Hp) polymorphisms on survival of RCC patients.

**Methods:** At interim analysis, 53 metastatic RCC patients were enrolled and Hp phenotypes were determined prospectively. Survival data was retrieved from the electronic patient files. Kaplan-Meier survival analyses were performed for disease-free survival (DFS), progression-free survival (PFS) after 1st- and 2nd-line therapy, and overall survival (OS).

**Results:** Fifty-eight percent of patients were male. Hp distribution was 19%, 49% and 32% for Hp 1-1, 2-1 and 2-2 phenotypes, respectively. Median follow-up since development of metastatic disease was 4.7 years (95% CI 3.5 – 6.5). Lowest DFS was found in patients with Hp 2-2 phenotypes. This was significant when Hp 2-2 phenotypes were compared with Hp 1-1/2-1 phenotypes (hazard ratio [HR] = 1.93 [95%CI 1.12 – 3.57], P = 0.0253). No significant difference between Hp phenotypes was noticed for PFS after 1st-line therapy. After 2nd-line therapy, longest PFS was observed in patients with Hp 2-1 and 2-2 phenotypes which was better compared with Hp 1-1 phenotypes. Lastly, OS was found to be longer in patients with Hp 2-1 and 2-2 phenotypes, although no significance was observed versus patients with Hp 1-1 phenotypes. Median durations of survival and HRs versus Hp 1-1 phenotypes are given in Table.

**Disclosure:** All authors have declared no conflicts of interest.

**Table: 906F Hp survival analysis**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Hp</th>
<th>N</th>
<th>Median survival</th>
<th>HR vs Hp 1-1</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-1</td>
<td>9</td>
<td>9</td>
<td>0.6 (0.2 – 4.3)</td>
<td>1</td>
<td>0.0616</td>
</tr>
<tr>
<td>2-1</td>
<td>19</td>
<td>23</td>
<td>2.3 (0.6 – 5.0)</td>
<td>0.73 (0.34 – 1.59)</td>
<td>0.7529</td>
</tr>
<tr>
<td>2-2</td>
<td>14</td>
<td>24</td>
<td>2.5 (0.1 – 2.6)</td>
<td>1.54 (0.60 – 3.97)</td>
<td>0.0011</td>
</tr>
<tr>
<td>PFS 1st-line (months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-1</td>
<td>16</td>
<td>26</td>
<td>14.7 (6.3 – 28)</td>
<td>0.90 (0.33 – 2.45)</td>
<td>0.4205</td>
</tr>
<tr>
<td>2-2</td>
<td>7</td>
<td>5</td>
<td>6.7 (4.2 – 52.2)</td>
<td>1.20 (0.40 – 3.54)</td>
<td>0.031</td>
</tr>
<tr>
<td>OS (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-1</td>
<td>10</td>
<td>19</td>
<td>11 (2.5 – 40)</td>
<td>0.61 (0.30 – 2.0)</td>
<td>0.07</td>
</tr>
<tr>
<td>2-2</td>
<td>11</td>
<td>15</td>
<td>8.4 (2.5 – 17.6)</td>
<td>0.56 (0.23 – 1.3)</td>
<td>0.126</td>
</tr>
</tbody>
</table>

**Conclusions:** interim analysis shows that Hp phenotype has prognostic potential, especially in DFS and PFS during 2nd-line therapy. Continuation of the research on this topic is warranted.

**Legal entity responsible for the study:** Ghent University

**Funding:** Ghent University

**Disclosure:** All authors have declared no conflicts of interest.

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**905F CORE-URO-01 study: comparison of safety and efficacy of pazopanib in first-line metastatic renal cell carcinoma (mRCC) with or without renal failure**

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**Background:** Pazopanib has been approved for first-line treatment of patients (pts) with mRCC based on the prospective randomized trial that enrolled only pts with adequate renal function. There are no data on the efficacy and toxicity of pazopanib in pts with renal insufficiency (RI).

The aim of this study is to investigate the effect of kidney function on treatment outcomes in pts treated with pazopanib for mRCC.

**Methods:** We retrospectively analyzed the data of the mRCC pts treated with pazopanib with respect to renal function in fourteen Italian institutions from January 2010 to June 2016. Baseline glomerular filtration rate (GFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula at the time of therapy initiation.

**Results:** Two hundred and twenty-nine pts with mRCC were included in this study: 128 pts in group A and 101 pts in group B. 68% of pts were male, median age was 67 years (34-88) and median CrCl was 49.7 ml/min in group A. In group B, 64% of pts were male, median age was 64 years (38-85) and median CrCl was 74 ml/min. Pts with MDRD ≥ 60 were more likely to have had a previous nephrectomy (83% vs 79%). Median PFS was 14 months (95% confidence interval [CI] 9.4-18.5) and 17 months for MDRD ≥ 60 in group A and B (p = 0.01). The disease control rate was 84% in group A, and 73% in group B (p = 0.1). About toxicity profile, no difference between the 2 groups was reported in terms of incidence of grade 1-2 (73% in group A and 74% in group B, p = 0.5) and grade 3-4 (24% vs 33% respectively, p = 0.2). Dose reductions are statistically more frequent in pts in group A (66% vs 36%), p = 0.04, despite the same percentage of pts in both groups started at dose of 800 mg/day.

**Conclusions:** Although in this study it is necessary to reduce the dose of pazopanib more frequent in pts with RI, kidney function at therapy initiation does not adversely affect the efficacy and safety of pazopanib.

**Legal entity responsible for the study:** Cristina Masini

**Funding:** None

**Disclosure:** All authors have declared no conflicts of interest.
Background: Pazopanib is characterized by a large interpatient variability in systemic drug exposure. As pazopanib trough levels (≥20.5 mg/L) are correlated with clinical outcome (Suttle et al, BJC 2014) in metastatic renal cell carcinoma (mRCC) patients, it is vital to identify factors that influence pazopanib pharmacokinetics (PK). The objective of the current analysis was to evaluate if single nucleotide polymorphisms (SNPs) in the metabolic pathway of pazopanib (i.e. CYP3A4, ABCB1 and ABCG2) affect systemic pazopanib concentrations.

Methods: We analyzed 97 patients who participated in 3 pazopanib PK studies. Starting point of the current analysis was a population PK model for pazopanib (Yu et al, Clin Pharmacokiniet 2017). Four SNPs located on 3 genes, that were associated with decrease of function were analyzed using real time PCR: CYP3A4 15389 C>T, (rs776746), ABCB1 3453 C>T, and the ABCG2 SNPs 421 C>A, and 345 G>A. The influence of these SNPs on pazopanib bioavailability and clearance (CL) was explored with NONMEM. Statistical significance was determined with the likelihood ratio test using the objective function value (OFV). Trough concentrations (Ctrough) at 6 weeks after start with doses of 400 to 800 mg once daily (OD), were simulated. A threshold Ctrough of 20.5 mg/L was used as reference.

Results: From 3 patients, insufficient DNA was isolated to run a PCR analysis. All SNPs were in Hardy-Weinberg equilibrium. Eleven patients (12%) had a variant allele at CYP3A4*22, all of whom were heterozygous. Incorporation of CYP3A4*22 in the NONMEM model resulted in a 35% lower CL for the variant carriers (0.18 L/h vs. 0.27 L/h, ΔOFV = 8.7; P = 0.001). Simulated median Ctrough of patients with CYP3A4*22 with 400 mg OD, 600 mg OD or 800 mg OD were 16 mg/L, 25 mg/L and 33 mg/L, respectively. Simulated Ctrough for the population excluding the CYP3A4*22 heterozygotes after 800 mg OD was 21 mg/L. No effect of the ABCB1 or ABCG2 SNPs on systemic concentrations were found.

Conclusions: Our analysis shows that CYP3A4*22 carriers have a clinically relevant lower pazopanib CL. Prospective analysis should point out whether carriers are at risk for more toxicity and require a lower pazopanib starting dose.

Legal entity responsible for the study: Erasmus MC, Rotterdam, The Netherlands

Funding: None

Disclosure: All authors have declared no conflicts of interest.

References:


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Background: Depressive symptoms have been associated with poorer OS in pts with mRCC (Primoso et al Behav Med 2015). In other malignancies, BPSD has also been linked to poorer OS, but in mRCC, this association is unclear.

Methods: From a single institution, clinicopathologic information from pts with mRCC diagnosed between 2001 and 2016 were collected. Corresponding data from an electronic survey tool was obtained, comprised of 22 core items spanning physical, practical, functional and emotional domains. Each item was self-assessed by the pt on a 5-point Likert scale. The cumulative score was used to characterize BPSD as either as low BPSD (function/mood) or high BPSD. Associations between BPSD level and clinicopathologic criteria (e.g., Heng risk) were interrogated, and OS was compared between patients characterized as low BPSD vs high BPSD.

Results: A total of 102 pts (28.4% F/71.6% M) were assessed with a median age of 63 (range, 24-80). 73.4 and 26.6% pts were characterized as having good/intermediate and poor risk by Heng criteria, respectively. 79.3% pts and 20.7% pts were characterized as having low and high BPSD, respectively. No association was found between BPSD and age or gender. However, married patients have a longer survival (48.65 mos vs 34.52 mos, P=0.07). Pts with poor risk mRCC were noted to have a higher BPSD as compared to pts with mild BPSD (75% vs 25%, P=0.22). Median OS in the overall cohort was 44.2 months (mos). Although not statistically significant, a trend towards prolonged OS in pts with low BPSD vs high BPSD was observed (45.81 mos vs 35.95 mos, P=0.8).

Conclusions: Our study suggests a potential link between Heng risk and BPSD, and further shows a compelling trend towards poorer OS in pts with higher BPSD. These results warrant confirmation in larger series. Targeted interventions to address elements related to BPSD have the potential to improve patient outcomes and should be developed.

Legal entity responsible for the study: City of Hope Comprehensive Cancer Center

Funding: None

Disclosure: All authors have declared no conflicts of interest.

References:

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Background: Because renal cell carcinoma (RCC) is diagnosed 75-80% with clear cell histology, there is little data on treatment and outcome of patients (pts) with non-clear RCC. They are reported to have a poorer prognosis and are often excluded from clinical trials. Here, we present data on papillary RCC, the most common non-clear cell subtype (10-15% of RCC).

Methods: The prospective German RCC-Registry includes pts with advanced or metastatic RCC at start of systemic first-line therapy. Data on patient and tumour characteristics, all systemic therapies and outcome are collected. More than 300 medical and uro oncologists are recruiting pts since 2007.

Results: Median age for pts with papillary RCC (n=92) at start of first-line therapy was 66 years. According to MSKCC risk category, pts were classified into 30% low, 55% intermediate and 2% high risk (12% unknown). From 2007 to May 2016 (data cut 2016) treatment changed. First-line, the use of sunitinib declined and the use of temsirolimus and pazopanib increased. Since 2011 (n=46), first-line treatments included 33% (n=15) temsirolimus, 30% (n=14) sunitinib and 22% (n=10) pazopanib. The most frequently used second-line treatments since 2011 (n=28) are sunitinib (36%, n=10, everolimus and pazopanib (18%, n=5 each), temsirolimus (11%, n=3 followed by axitinib and sorafenib (7%, n=2 each). The most frequently used first - second line combination - second line strategies (first-line since 2011, n=23) are mTOR inhibitors (temsirolimus) -> TKI (35%, n=8) and TKI -> TKI (26%, n=6) (TKI: sunitinib, axitinib, pazopanib or sorafenib). Updated data (data cut May 2017) including rivaroxaban will be presented. Median progression-free survival (PFS) for the first-line was 6.1 months (95% CI 4.0 - 9.9) for pts with papillary RCC versus (vs) 8.6 (7.7 - 9.7) for pts with clear cell RCC (crcc, n=772). For the second-line, median PFS was 3.7 (2.3 - 4.9) vs 4.8 (4.2 - 5.8) (papillary vs crcc). Median overall survival (OS) was 12.7 (8.5 - 23.8) vs 20.8 (19.1 - 23.8) (papillary vs crcc).

Conclusions: We show first - and second-line treatment of pts with advanced papillary RCC. Our data indicate that prognosis for pts with papillary RCC might be inferior to that of pts with clear cell RCC.

Clinical trial identification: NCT00610012

Legal entity responsible for the study: IOMEDICO AG

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References:
910P Exome sequencing of tumor samples from S1107 “Randomized phase II evaluation of tivantinib and tivantinib in combination with erlotinib in patients with papillary renal cell carcinoma (pRCC)”

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Background: pRCC is associated with activation of MET pathway, overexpression of EGFR and inferior responses to VEGF inhibition than clear cell RCC. In S1107 we randomized patients (pts) with advanced pRCC and 0-1 prior systemic therapy to MET inhibitor tivantinib at 360 mg BID (Arm 1) or tivantinib 360 mg BID plus EGFR inhibitor erlotinib at 150 mg daily (Arm 2). 66% of pts had no prior systemic therapy, 6% had type 1 pRCC, 42% had type 2, and 52% had no subtype assigned. The study was closed at interim analysis after 55 pts were enrolled and 0% RR was noted. Median PFS was 2.0 and 3.3 months, and OS was 10.3 and 11.3 months in Arms 1 and 2 respectively. These results were inferior to previously reported clinical trials with pRCC. To better understand these outcomes we performed whole exome sequencing of tumor samples collected from pts participating in this study.

Methods: Exome of 16 pts were successfully sequenced using Agilent SureSelect probes. The mean coverage of target regions ranged from 45x to 91x. Only reads aligned to exon regions were collected. Only matching normal tissues were collected, but MET amplification was suspected in 3 pts. 1107 patient cohort had a high proportion of pts with molecular subtypes not driven by MET abnormalities and would not be expected to respond well to MET inhibition. Although MET remains a reasonable therapeutic target in pRCC, care must be taken to develop effective therapeutic strategies in this uncommon type of RCC.

Results: Most of the mutations were unique to individual pts indicating high diversity of variants in this patient cohort. Only 1 MET mutation was ascertained affecting tyrosine kinase domain. 29 mutations were associated primarily with type 2 pRCC included CDKN2A, PRDM1, SETD2, KDM6A, FAT1, NFI, CUL. No EGFR and FH mutations were detected. The most affected pathways included WNT, cadherin and miRNA 221-3p. Somatic copy number variation was challenging to obtain since no matching normal tissues were collected, but MET amplification was suspected in minority of cases.

Conclusions: S1107 patient cohort had a high proportion of pts with molecular subtypes not driven by MET abnormalities and would not be expected to respond well to MET inhibition. Although MET remains a reasonable therapeutic target in pRCC, careful selection of pts exhibiting MET alterations is required to better benefit from therapy with MET inhibitors.

Clinical trial identification: NCT01689793

Legal entity responsible for the study: Southwest Oncology Group

Funding: (NIH/NCTN CA180888;CA180819;CA180820).


911P Patients (pts) with metastatic non-clear cell renal cell carcinoma (mccRCC) treated with Nivolumab (Nivo) based immunotherapy as advanced treatment (ATL) line: analysis of a national early access program (EAP)

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Background: Immunotherapy with the anti-PD1 Nivo is a standard ATL for clear cell RCC, but has no proven activity in the rare variant of mRCC, limited (case reports). We aimed to report the activity of Nivo in mccRCC treated per a national EAP.

Methods: Records from consecutive mccRCC pts treated with Nivo ATL per a national EAP in 6 centers were retrospectively reviewed. We report the clinical benefit, progression free survival (PFS), overall survival (OS), and toxicity.

Results: Between 7/2015 – 12/2016, 16 mccRCC pts (median age 64, male 68%; papillary type 38%, n = 6; chromophobe 44%, n = 7; undifferentiated 12%, n = 2; pure sarcomatoid 6%, n = 1); 62% (n = 10) were treated with second line Nivo, and 38% (n = 6) as third and fourth line. Heng risk was good/intermediate/poor in 6% (n = 1)/75% (n = 12)/19% (n = 3). Clinical benefit (stable disease + partial response) was 37% (4 partial response and 2 stable disease). Median PFS was 3.5 months (mos). After a median follow up time of 8 mos, 100% of the pts with a clinical benefit are still with a benefit and on treatment (range 5-18mos). Most pts (69%, n = 11) are alive, with median OS not reached. Toxicity was mild grade 1-2 in the majority of pts (56%, n = 9).

Conclusions: Nivo as ATL may be active in mccRCC pts, and associated with durable responses and predictable mild toxicity. Future and larger studies are needed to assess the activity of immunotherapy in this uncommon type of mRCC.

Legal entity responsible for the study: the author

Funding: None

Disclosure: All authors have declared no conflicts of interest.

912P Cabozantinib for the treatment of patients with metastatic variant histology renal cell carcinoma (vhRCC): a retrospective study

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Background: Cabozantinib (C) prolongs overall survival (OS) and progression-free survival (PFS) in patients with metastatic clear-cell renal cell carcinoma (ccRCC) that progressed on first-line VEGFR-TKI. No standard of care systemic therapy exists for the management of patients with metastatic vhRCC.

Methods: This is a retrospective, IRB approved study of patients with vhRCC who received cabozantinib at MD Anderson Cancer Center from January 2014-January 2017. Information collected from the medical records included the baseline characteristics, toxicity, dose reductions, and OS. A blinded radiologist assessed the radiographic response using RECIST v1.1. Descriptive statistics, the Kaplan Meier method and the log rank test were applied using Microsoft Excel and GraphPad Prism version 6 software.

Results:

Table: 912P

<table>
<thead>
<tr>
<th>Gender</th>
<th>N = 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>26</td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>58.4 years (25-81)</td>
</tr>
<tr>
<td>Prior Nephrectomy</td>
<td>27 (90%)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Papillary</td>
<td>6</td>
</tr>
<tr>
<td>(P17) Chromophobe (Ch1)</td>
<td>3</td>
</tr>
<tr>
<td>Other:</td>
<td>6</td>
</tr>
<tr>
<td>unclassified</td>
<td>3</td>
</tr>
<tr>
<td>translocation</td>
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</tr>
<tr>
<td>sarcomatoid (sar)</td>
<td>1</td>
</tr>
<tr>
<td>mucinous</td>
<td>1</td>
</tr>
<tr>
<td>tubulospindle</td>
<td>1</td>
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<tr>
<td>cell1</td>
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</tr>
</tbody>
</table>

PFS: 23/5

Number of Prior Therapies 0 1 2 3 4

Median (range) 8.6 months (2.5-17.0)

Tyrosine Kinase Inhibitor

Disclosures: M.T. Campbell: Served on advisory boards for Esai, AstraZeneca. M.A. Bilen: Advisory Board for Exelixis. C. Duran: Served as a consultant and has served on advisory boards for Discovery, AstraZeneca.

Funding: None


Funding: None

Disclosure: All authors have declared no conflicts of interest.
Avelumab had a manageable safety profile and demonstrated clinical activity in patients with platinum-treated mACC. Here, we report an updated analysis of avelumab in patients (pts) with mACC, representing the largest prospective monotherapy study performed to date in this rare cancer with limited therapeutic options.

Methods: In a phase 1b cohort (NCT01772004), pts with mACC and prior platinum-based therapy received avelumab at 10 mg/kg Q2W until progression, unacceptable toxicity, or withdrawal. Prior and ongoing treatment with mitotane was permitted. Tumors were assessed every 6–8 weeks (RECIST v1.1). Endpoints included safety (NCI-CTCAE v4.0), best overall response, objective response rate (ORR), progression-free survival (PFS), and overall survival (OS).

Results: As of Dec 31, 2016, 30 pts from 6 countries received avelumab for a median of 3.4 mos (0.5–24.8). Median follow-up was 16.5 mos (11.7–27.6); 5 pts (10.0%) remained on treatment. Median age was 50 y (range 21–71) and median time since diagnosis of metastatic disease was 14.5 mos (24.8%). 2 pts (4.0%) had received ≥2 prior lines of treatment for advanced disease (median 1, range 0–6). 41 pts (82.0%) had a treatment-related adverse event (TRAE) of any grade; the most common (≥15%) were nausea (20.0%) and fatigue (18.0%). 8 pts (16.0%) had a grade ≥3 TRAE, of which only increased ALT (4.0%) occurred in >1 pt. 12 pts (24.0%) had an immune-related AE of any grade. Median PFS was 2.6 mos (95% CI 1.4–4.0). Median OS was ongoing in 1 pt at data cutoff. 21 pts (42.0%) had stable disease as best response (disease control rate 48.0%). Median PFS was 2.6 mos (95% CI 1.4–4.0). Median OS was 10.6 mos (95% CI 7.4–not estimable) and the 12-mo OS rate was 47.0% (95% CI 31.8–60.9). Responses occurred in 2 pts with PD-L1+ tumors and 1 PD-L1− (<5% tumor cell cutoff). In PD-L1+ (n = 12) vs PD-L1− (n = 30) subgroups, median PFS was 5.5 vs 1.7 mos (HR 0.66, 95% CI 0.3–1.4) and median OS was 14.4 vs 11.5 mos (HR 0.82, 95% CI 0.3–2.2), respectively.

Conclusions: Avelumab had a manageable safety profile and demonstrated clinical activity in pts with platinum-treated mACC.

Clinical trial identification: NCT: NCT01772004 Protocol: EMR 100070-001

Legal entity responsible for the study: Pfizer Inc., New York, NY, USA; Merck KGaA, Darmstadt, Germany.

Disclosure: C. Le Tourneau: Provided a consulting role for MSD, Bristol-Myers Squibb, Novartis and AstraZeneca and received honoraria from Merck Serono and AstraZeneca. C. Zarwan: Provided an advisory role for Revere Pharmaceuticals and consulting for Perceptive Informatics. C. Hoimes: Provided an advisory role for Seattle Genetics and Eisai, and participated in speaker’s bureau’s for Bristol-Myers Squib and AstraZeneca. C. Zarwan: Provided an advisory role for Revere Pharmaceutics and consulting for Perceptive Informatics. K. Chin: Employee of EMD Serono Inc. All other authors have declared no conflicts of interest.

H.J. Grote 7, A. von Heydebreck 8, K. Chin 9, J. Gulley 10

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Abstracts: Avelumab in patients with metastatic adrenocortical carcinoma (mACC): Results from the JAVELIN solid tumor trial

Background: Avelumab is a human anti–PD-L1 IgG1 antibody that has shown promising clinical activity in multiple tumor types, and is approved in the US for the treatment of metastatic Merkel cell carcinoma. Here, we report an updated analysis of avelumab in patients (pts) with mACC, representing the largest prospective monotherapy study performed to date in this rare cancer with limited therapeutic options.

Methods: In a phase 1b cohort (NCT01772004), pts with mACC and prior platinum-based therapy received avelumab at 10 mg/kg Q2W until progression, unacceptable toxicity, or withdrawal. Prior and ongoing treatment with mitotane was permitted. Tumors were assessed every 6–8 weeks (RECIST v1.1). Endpoints included safety (NCI-CTCAE v4.0), best overall response, objective response rate (ORR), progression-free survival (PFS), and overall survival (OS).

Results: As of Dec 31, 2016, 30 pts from 6 countries received avelumab for a median of 3.4 mos (0.5–24.8). Median follow-up was 16.5 mos (11.7–27.6); 5 pts (10.0%) remained on treatment. Median age was 50 y (range 21–71) and median time since diagnosis of metastatic disease was 14.5 mos (24.8%). 2 pts (4.0%) had received ≥2 prior lines of treatment for advanced disease (median 1, range 0–6). 41 pts (82.0%) had a treatment-related adverse event (TRAE) of any grade; the most common (≥15%) were nausea (20.0%) and fatigue (18.0%). 8 pts (16.0%) had a grade ≥3 TRAE, of which only increased ALT (4.0%) occurred in >1 pt. 12 pts (24.0%) had an immune-related AE of any grade. Median PFS was 2.6 mos (95% CI 1.4–4.0). Median OS was 10.6 mos (95% CI 7.4–not estimable) and the 12-mo OS rate was 47.0% (95% CI 31.8–60.9). Responses occurred in 2 pts with PD-L1+ tumors and 1 PD-L1− (<5% tumor cell cutoff). In PD-L1+ (n = 12) vs PD-L1− (n = 30) subgroups, median PFS was 5.5 vs 1.7 mos (HR 0.66, 95% CI 0.3–1.4) and median OS was 14.4 vs 11.5 mos (HR 0.82, 95% CI 0.3–2.2), respectively.

Conclusions: Avelumab had a manageable safety profile and demonstrated clinical activity in pts with platinum-treated mACC.

Clinical trial identification: NCT: NCT01772004 Protocol: EMR 100070-001

Legal entity responsible for the study: Pfizer Inc., New York, NY, USA; Merck KGaA, Darmstadt, Germany.

Disclosure: C. Le Tourneau: Provided a consulting role for MSD, Bristol-Myers Squibb, Novartis and AstraZeneca and received honoraria from Merck Serono and AstraZeneca. C. Zarwan: Provided an advisory role for Revere Pharmaceuticals and consulting for Perceptive Informatics. C. Hoimes: Provided an advisory role for Seattle Genetics and Eisai, and participated in speaker’s bureau’s for Bristol-Myers Squib and AstraZeneca. C. Zarwan: Provided an advisory role for Revere Pharmaceutics and consulting for Perceptive Informatics. K. Chin: Employee of EMD Serono Inc. All other authors have declared no conflicts of interest.
Methods: We utilized a single institution database of patients diagnosed with metastatic GCTs between January 1990 and December 2013 who were treated with chemotherapy at Princess Margaret Cancer Centre. The peripheral blood count prior to first line chemotherapy was used to calculate the derived NLR (absolute neutrophil count divided by the total white blood cell count minus the absolute neutrophil count). Predictive accuracy was assessed as the association between NLR and overall survival and was evaluated using a Cox proportional hazard model adjusted for the International Germ Cell Cancer Collaborative Group (IGCCCG) risk classification. Discriminatory accuracy was evaluated by determining the area under the receiver operating characteristic curve (AUROC) for survival at 5 years. The optimal cut-off for NLR selection was chosen based on a highest AUROC.

Results: In total, 475 patients were identified of which NLR data were available from 354 (75%) patients. Among these, 63% were good risk, 23% intermediate risk and 15% poor risk. The 5-year survival for good, intermediate and poor risk groups was 96.3%, 92.4% and 62.9%, respectively.

Conclusions: A high NLR is associated with an adverse survival in patients with metastatic GCTs undergoing first line chemotherapy and provides moderate discriminatory accuracy in this setting. The utility of NLR apparently appears in patients with IGCCCG high risk disease.

Legal entity responsible for the study: Senior authors, Dr. Jeremy Lewin and Dr. Eitan Amir

Disclosure: All authors have declared no conflicts of interest.

916P Biological assessment of viable germ cell tumor (VT) in patients (pts) with seminoma (S) and non-seminoma (NS) using miR371

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Background: The pathological constitution of residual nodes after chemotherapy or of the borderline enlarged retroperitoneal (RP) lymph nodes in clinical stage I (CSI) germ cell tumor (GCT) pts on surveillance is challenging, especially in tumor markers (TM) negative pts. Currently, accurate assessment requires pathological correlation with RPLND or clinical follow-up to establish a pattern of growth. A plasma-based approach to identify patients with VT would be uniquely valuable.

Methods: Formalin-fixed paraffin embedded (FFPE) and plasma from GCTs-patients were used for miRNAs extraction. Non-cancer FFPE testicular tissue and plasma from healthy volunteers were used as negative controls. miR371 expression was detected by RT-PCR and relative expression calculated by the 2-DeltaCt method. miR-93-3p was used as positive internal control. Results were analyzed for associations with clinicopathological features using Fisher’s exact test.

Results: miR371 was over-expressed in all the primary testicular (n = 4) and mediastinal (n = 3) samples while it was undetectable in the atrophic testis (n = 1) and mediastinal or gonadal teratoma (n = 2), confirming the applicability of the method to the FFPE samples. 21 metastatic samples were analyzed: 2 lung, 1 brain, 17 lymph nodes and 1 IVC tumor thrombus. The samples were collected prior to (n = 2) or after (n = 12) chemotherapy, while 7 pts were treated only with surgery. miR371 was undetectable in any samples (0/9) with no VT on pathological examination and over-expressed in 11/12 (91.6%) of those with viable GCT (OR 145.7; p < 0.001). 90% of pts with positive miR-371 had negative TM (100% of S and 75% of NS) while no pts with negative miR-371 had positive TM. Plasma miR-371 also showed high correlation with VT (Table).

Table: 916P

<table>
<thead>
<tr>
<th>Pts</th>
<th>Initial Stage</th>
<th>Stage at the suspicious relapse</th>
<th>Histology</th>
<th>miR71</th>
<th>Evidence of VT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IIA</td>
<td>S</td>
<td>+</td>
<td>+ (RPLND)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>IIA</td>
<td>S</td>
<td>–</td>
<td>(negative PCT scan)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>IIA</td>
<td>S</td>
<td>–</td>
<td>(regressing CT scan)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>IIA</td>
<td>NS</td>
<td>+</td>
<td>(progressing CT scan)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: Elevated plasma levels of miR-371 correlate with the presence of active germ cell malignancy. These encouraging findings suggest that plasma miR371 levels may lead to biological rather than radiographic assessment of the presence of active GCT in patients with S and NS.

Legal entity responsible for the study: Lucia Nappi

Disclosure: All authors have declared no conflicts of interest.

917P A single centre retrospective review of testosterone deficiency in germ cell cancer patients

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Background: Testosterone deficiency syndrome (TDS) is frequently described in men treated for germ cell cancer with rates quoted between 31 and 38% (Huddart et al 2005). Observational studies show that TDS reduces quality of life and carries cardiovascular, metabolic and bone health risks. At our institute we observed that men with symptoms of TDS and ‘low normal’ testosterone (T) (8.6 – 12 nmol/L) were not reliably recognised.

Methods: We collected retrospective data from all germ cell cancer referrals to the Bristol Cancer Institute from 2011 – 2016. We documented age, treatment, at least one random T level within a year of diagnosis (grouped into < 8.8, 8.8 – 12 > 12 nmol/L), details of symptoms and treatment of TDS.

Results: Data was collected on 462 patients (36 excluded with non germ cell diagnoses and 26 excluded due to T never being measured). Median age was 36 years (range 17 – 89) with 85% of patients aged under 50. 58% of men had seminoma, 32% non-seminoma and 10% combined germ cell cancer. 41% of all patients had a T level < 12 nmol/L at first measurement (32% of 20 – 29 year olds, 42% of 30 – 49 and 58% of 50 – 59 year olds) and 16% had T < 8 nmol/L. T therapy was prescribed in 19% of patients. Men receiving adjuvant carboplatin had the highest rate of T therapy (23%) compared with patients on surveillance (18%) and BEP or EP chemotherapy (14%).

Conclusions: In this retrospective series 41% of patients had at least one total T value < 12 nmol/L. 19% received replacement. A TDS diagnosis should not be based on a single measurement but regardless of age, once T falls to < 15 nmol/L, severity of TDS sequelae correlate with further decline (Morgentaler et al 2016). There is a range of what is regarded as normal T and it declines naturally with age. Recognition and management of late effects is important in men with curable cancer and diagnosis must be individualised; addressing symptoms alongside biochemical parameters. This is reflected by germ cell cancer social media websites where men frequently describe serum T in the defined normal range with symptoms of TDS. Further prospective multi-centre studies could better define the prevalence of TDS in these patients and be used to inform a standard diagnostic approach.

Legal entity responsible for the study: Jeremy Braybrooke

Disclosure: None

918TP Pembrolizumab and nanoparticle albumin bound paclitaxel (nab-paclitaxel) for metastatic urethral carcinoma (UC) after chemotherapy failure: the open-label, single-arm, phase 2 PEANUT study

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Background: Pembrolizumab (pembro) is a new standard of care in chemotherapy (CT)-pretreated UC patients (pts) and nab-paclitaxel (nPa) has shown one of the highest activities among CT options in UC. Their combination may overcome resistance to immuno therapy (IT) and result in longer delay in the time to disease progression (PD). We will explore dynamic biomarkers of response to CT+IT.

Trial design: In an open-label, single-arm, single-center, phase 2 trial, pts receive pembro 200 mg intravenously (IV) on D1 and nPa at the dose of 125 mg/m² IV on D1 and D8. Cycles are repeated every 3 weeks until PD or onset of unacceptable toxicity. Key inclusion criteria are: predominant UC, failure of ≥ 2 platinum-based CT for metastatic disease (≥2s- or ≥3l- only). Neadjuvant/adjuvant CT is counted if relapse occurred ≤ 6 months of the last CT cycle. Response is evaluated by RECIST criteria v.1.1 every 2 cycles. PD-L1 expression will be assessed at the study conclusion on both immune cells (IC) and tumor cells at a centralized lab (Quotok, Goleta, CA USA). The primary endpoint of the study is the progression-free survival (PFS). The target is to detect an improvement in the median PFS from ≥ 3.0 months (H0) to ≥ 5.0 months (H1). To achieve 90% power with a one-sided non-parametric test at the 10% significance level,
we estimated that 64 pts must be accrued over 18 months, with follow-up duration of 12 months. PFS will be also analyzed according to the PD-L1 expression. Should the above investigation suggest that the treatment benefit is stronger in PD-L1 þ pts, there is the option to expand this cohort to a maximum of 50 pts. As such, we estimate 85.1% power to detect the target improvement in PFS. The design of cohort expansion will rely on predictive power (PP) calculation: a PP ≥ 50% will be regarded as promising. Translational analyses will include multiparametric flow cytometry of blood samples, gene expression (RNA-seq, Illumina HiSeq) and mutation profiling of tumor samples (Ion Torrent Personal Genome Machine). These profiles will be matched with response to treatment and PFS/overall survival (EudraCT number 2017-000579-10).

Clinical trial identification: EudraCT number 2017-000579-10. Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale dei Tumori. Funding: Merck. Disclosure: All authors have declared no conflicts of interest.

**919TIP** Pembrolizumab ± chemotherapy versus chemotherapy in advanced urothelial cancer: Phase 3 KEYNOTE-361 trial


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Background: Inhibitors of programmed death 1 (PD-1) and its ligand PD-L1 have demonstrated clinical activity in patients (pts) with advanced urothelial cancer. Pembrolizumab ± chemotherapy may represent a promising strategy. The rationale for this Phase III trial is based on the results of KEYNOTE-028 and KEYNOTE-158 showing the efficacy and tolerability of the combination of pembrolizumab and chemotherapy for pts with locally advanced or metastatic urothelial cancer. The KEYNOTE-361 study is designed to compare the clinical benefit of pembrolizumab ± chemotherapy versus chemotherapy in pts with advanced urothelial cancer. The primary endpoint is objective response rate and safety. Efficacy will be compared for pembrolizumab ± chemotherapy versus chemotherapy. Patient accrual is ongoing; 1 interim efficacy analysis is planned.

Clinical trial identification: NCT02855305; July 29, 2016. Legal entity responsible for the study: Merck & Co., Inc.

Funding: Merck & Co., Inc.

Disclosure: T. Powles: Received research funding from Merck, AstraZeneca and Roche; honoraria and travel expenses reimbursement from Pfizer, Merck, AstraZeneca, Roche, and Novartis. J.E. Gschwend: Served as advisor for and received honoraria and reimbursement for travel expenses from Bayer, Bristol-Myers Squibb, Janssen, Novartis, Pfizer, and Roche. Y. Loriot: Served as advisory board member for Astellas, Janssens, Roche, MSD, AstraZeneca; received research funding and honoraria from Sanofi and received reimbursement for travel expenses from Roche. M. Abdelbassat: Have been an advisory board member for Pfizer, Merck, Novartis, served on speakers’ bureaus for Pfizer and Roche, received honoraria from Pfizer, Merck, Roche, Novartis, AstraZeneca, and been reimbursed for travel expenses by AstraZeneca. M. Fleming: Served as advisory board member and as speakers’ bureau member for Genentech. M. Markus: Served as consultant/advisor for Biotheranostics. D. Feng: Employed by and own stock in Merck & Co., Inc. C. Poethen: Employed by and received compensation from Merck & Co., Inc. J. Bellmunt: Served as consultant/advisor to Eisai and received research funding from BIND Biologics, Bristol-Myers Squibb, Genentech, Novartis, and Oncogenex. All other authors have declared no conflicts of interest.

**920TIP** Afatinib in patients with advanced or metastatic urothelial carcinoma (UC) with genetic alterations in ERBB receptors 1–3 who failed on platinum-based chemotherapy: The Phase II LUX-Bladder 1 trial


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Background: First-line treatment of patients (pts) with advanced or metastatic UC consists of platinum-based chemotherapy (CT), and currently, there is no well-established therapy following CT failure. Recently, checkpoint inhibitors have shown clinical benefit in this setting, and are likely to become a future standard of care. However, to date, no other targeted therapies have shown significant clinical activity. Given that ~20% of UCs harbour ERBB receptor alterations or abnormalities, the blockade of the ERBB pathway may be an effective therapeutic strategy. Indeed, afatinib, an irreversible ERBB family blocker, demonstrated activity in a Phase II trial in a subgroup of pts with UC harbouring ERBB2/ERBB3 alterations. These data provide rationale for the current Phase II trial assessing afatinib in pts with UC, molecularly selected for ERBB receptor alterations (LUX-Bladder 1; NCT02780687).

Trial design: The Phase II, single-arm LUX-Bladder 1 trial evaluates the efficacy and safety of afatinib in pts with UC harboring ERBB2/ERBB3 mutations or ERBB2 amplification (Cohort A), or EGFR amplification (Cohort B). Eligible pts are ≥ 18 years of age, with histologically confirmed advanced/metastatic UC of the urinary tract not amenable to surgery and progression during or after platinum-based CT (previous immunotherapy allowed). ECOG PS 0–1, with archival tissue samples available for pre-screening biomarker analysis. Pts will receive oral afatinib 40 mg/day until disease progression or discontinuation for other reasons. Cohort A will enroll in two stages, with Stage (S) 2 enrolment depending on afatinib anti-tumour activity in S1. The primary endpoint marker analysis. Pts will receive oral afatinib 40 mg/day until disease progression or discontinuation for other reasons. Cohort A will enroll in two stages, with Stage (S) 2 enrollment depending on afatinib anti-tumor activity in S1. The primary endpoint will be patient progression-free survival (RECIST v1.1). Secondary endpoints include PFS, OS, disease control rate, duration of response and tumour shrinkage. These endpoints will also be explored in Cohort B. Safety and biomarkers will be assessed in both cohorts. The trial commenced in June 2016. Recruitment is ongoing in Spain and planned in two additional European countries; planned enrolment: Cohort A: ~70 pts (S1, n = 25; S2, n = 45); Cohort B, ~10 pts.

Clinical trial identification: NCT02780687; 1200.261. Legal entity responsible for the study: Boehringer Ingelheim.

Funding: Boehringer Ingelheim.

A Phase III, randomized, double-blind, multicenter study of adjuvant nivolumab vs placebo in patients (pts) with high-risk invasive urothelial carcinoma (UC; CheckMate 274)

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Background: Standard of care for muscle-invasive bladder cancer (predominant form of UC) is cisplatin-based neoadjuvant chemotherapy followed by radical cystectomy. Pelvic node dissection or cystectomy + pelvic node dissection alone if cisplatin-ineligible. Some pts undergo radical resection followed by adjuvant cisplatin-based chemotherapy. Many pts are not candidates for adjuvant chemotherapy or are not treated due to lack of proven survival benefit. UC of the ureter or renal pelvis is typically managed with nephroureterectomy. Despite surgery + chemotherapy, pts with invasive UC are at high risk of recurrence and death. Based on the efficacy and safety of the programmed death-1 (PD-1) inhibitor nivolumab for metastatic or unresectable UC progressing despite chemotherapy (CheckMate 032 and 275), we are conducting an international, phase III study of adjuvant nivolumab vs placebo in pts with invasive UC (originating in bladder, ureter, or renal pelvis) following resection (NCT02632409).

Trial design: Pts must have had radical surgical resection ± cisplatin-based neoadjuvant chemotherapy within the past 120 days and be disease-free (by imaging) ≤4 weeks before randomization. Pts who did not receive cisplatin-based neoadjuvant chemotherapy must be ineligible for or refuse adjuvant cisplatin. Tumor tissue must be available for biomarker analysis. Pts are ineligible if they had partial cystectomy or partial nephrectomy, or secondary treatment after surgical removal of UC (eg, cisplatin-based adjuvant chemotherapy), prior malignancy within 3 years except those treated with curative intent and in remission, or any condition requiring systemic treatment with immunosuppressants (eg, corticosteroids) within 2 weeks of treatment. Recruitment began in February 2016. Co-primary end points: Disease-free survival (defined as the time between date of randomization and date of first recurrence or death) in pts with tumors expressing ≥1% PD-1–ligand 1 and in all randomized pts. Secondary endpoints: Non-urothelial tract recurrence-free survival, disease-specific survival, overall survival.

Clinical trial identification: NCT02632409

Legal entity responsible for the study: Bristol-Myers Squibb

Funding: Bristol-Myers Squibb


A Phase 2 Biomarker driven trial with Nivolumab and Ipilimumab or VEGFR tkis in naïve metastatic kidney cancer: the BIONIKK trial

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Background: Nine targeted agents have been approved for metastatic clear cell renal cell carcinoma (mccRCC) in the last 10 years, including VEGFR-tyrosine kinase inhibitors (TKI), mTOR inhibitors and checkpoint inhibitor (CI). Combination of CI nivolumab and ipilimumab is currently compared to sunitinib in a randomised phase III trial in first-line setting. While treatment opportunities of mccRCC are moving rapidly biomarker to select patients to receive TKI or CI are still lacking. Based on transcriptomic analysis, we have defined four distinct molecular groups (crrcc 1 to 4) in patients with mccRCC treated with sunitinib. These groups were characterized by distinct responses to sunitinib as well as distinct immune cell compositions and inhibitory receptor expressions.

Trial design: The proof of concept study BIONIKK is a French multicentric randomised phase II designed to assess the use of molecular groups to select treatment in first-line mccRCC. Molecular group is determined on frozen tumor sample within 2 weeks. Treatment is then allocated between TKI and nivolumab plus ipilimumab for crrcc 2 and 3 between nivolumab alone and nivolumab plus ipilimumab for crrcc 1 and 4. Main objective is to assess efficacy of each treatment arm according to molecular group. Primary endpoint is overall response rate using RECIST 1.1. Main secondary endpoints include PFS, OS and their relationship to exploratory biomarkers. These latter include protein and gene expression analyses of tumor microenvironment (TME) from formalin-fixed and paraffin-embedded tumor samples. In addition, phenotype and functional status of peripheral blood lymphocytes will be analysed with flow cytometry before and during treatment. A Bayesian model was used to avoid independent analyses of the effect of drugs using hierarchical borrowing. Biomikk is not designed to be conclusive on the superiority of any treatment but will generate important hypotheses on putative biomarkers to select patients to receive TKI, CI alone or in combination. From this point of view, Biomikk is the first biomarker-driven trial in first line metastatic ccrcc.

Clinical trial identification: NCT02960906 First received: August 18, 2016

Legal entity responsible for the study: Association Pour La Recherche des Therapeutiques Innovantes en Cancérologie

Funding: Association Pour La Recherche des Therapeutiques Innovantes en Cancérologie and Bristol-Myers Squibb

Disclosure: S. Oudard: Honoraria fees from Astellas, Pfizer, Sanofi, Janssen, Bristol-Myers Squibh, Pfizer, Novartis, Astellas, Sanofi, Jansen, Roche. All other authors have declared no conflicts of interest.
A phase 2 study of investigational TORC1/2 inhibitor TAK-228 and TAK-228 plus investigational PI3Ks-selective inhibitor TAK-117 vs everolimus in adults with advanced or metastatic clear-cell renal cell carcinoma (cRCC) that has progressed on VEGF-targeted therapy


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Background: VEGF-targeted therapies are the cornerstone of first and subsequent lines of therapy in cRCC; however, resistance develops almost invariably. A proven therapeutic intervention in cRCC is treatment with the allosteric mTOR inhibitor everolimus, which only partially inhibits TORC1 and thus results in increased phospho-AKT activity and paracrine hyperactive signaling. TAK-228, a highly selective ATP-competitive TORC1 and TORC2 inhibitor, has shown promising antitumor activity and acceptable safety in cRCC. In a pooled analysis of 2 prior studies of 41 patients (pts) with cRCC, TAK-228 treatment resulted in 1 CR, 5 PR and 21 pts with SD, 13 pts who achieved ≥ SD had prior treatment with a rapalog. The median duration of overall response was 250 d (range, 55–1614). The most common AEs were fatigue, nausea and hyperglycemia. Also, combination of TAK-228 with TAK-117, a selective inhibitor of PI3Kα, has shown more complete and prolonged inhibition of TORC1 and TORC2. This phase 2, open-label, randomized study will evaluate the efficacy and safety of TAK-228 and TAK-228 + TAK-117 vs everolimus in pts with advanced or metastatic cRCC that have progressed on or after VEGF-targeted therapy (NCT02724020).

Trial design: 189 pts will be randomized 1:1 to TAK-228 30 mg once-daily on d 1, 8, 15, 22 with a light meal; TAK-228 4 mg once-daily (QD) + TAK-117 200 mg QD on d 1–3, 8–10, 15–17, 22–24 on an empty stomach; or everolimus 10 mg QD, in 28-d cycles. Pts will be stratified by number of prior therapy lines and IMDC risk category. Pts with histologically confirmed advanced/metastatic cRCC, ≥ 1 prior line of VEGF-targeted therapy with PD, KPS ≥70%, and adequate organ function, but no CNS metastasis or prior therapy with agents that target PI3K, AKT, or mTOR are eligible. Pts in the everolimus arm who progress may crossover. An interim futility analysis will be conducted after 30 pts in each arm have received 2 treatment cycles. Primary endpoint is PFS. Secondary endpoints are OS, TTP, ORR, CBR, safety, and QoL. As of January 24, 2017, 54 pts have been screened.

Clinical trial identification: NCT02724020

Legal entity responsible for the study: AstraZeneca

Funding: Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited


Phase IIb trial of interleukin-2 (IL-2) and nivolumab in metastatic clear cell renal cell cancer (RCC)

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Background: High dose Interleukin-2 (HD IL-2) immunotherapy is standard therapy in suitable patients (pts) with metastatic clear cell RCC who have good performance status. HD IL-2 is unique among RCC, therapy response assessments (TRA) and disease control rates (DCR) with a median duration of each of these responses of 12 years. However, the complete response (CR) proportion for HD IL-2–monotherapy is only 7–9%. There is an urgent need to evaluate HD IL-2 combination therapies that could increase the response proportion. IL-2 promotes early steps in the lymphocyte activation cascade, increases trafficking of cytotoxic T lymphocytes to the tumor and induces Th1 differentiation of CD4+ T helper cells. Nivolumab, an immune checkpoint inhibitor, blocks the interaction between PD-1 on activated T cells and its ligands that are expressed on immune cells and tumor cells. We hypothesize that the combination of HD IL-2 and a PD-1 inhibitor would elicit a potent synergistic anti-cancer immune response reflected in improved response proportion and survival with acceptable toxicity in pts with metastatic clear cell RCC.

Trial design: This multi-site Ib/II trial will determine safety and efficacy of HD IL-2– in combination with nivolumab for RCC. Pts with metastatic clear cell RCC, prior systemic therapies and candidates for HD IL-2 and for nivolumab are eligible. Pts will be treated with HD IL-2 (4,000,000 U/kg/dose every 8 hours for up to 14 doses) on Days 1-5 and again on Days 15-19, with nivolumab (240 mg IV every 14 days) starting on Day 8 ± 3 wk. Pts will continue on nivolumab every 2 wk for up to 48 wk barring in tolerable toxicities or consent withdrawal or progressive disease. Nivolumab may potentially be continued beyond first progression. The primary endpoint/objective of the phase Ib portion of the trial is safety of the combination/immune mediated grade 3/4 events of interest. The primary endpoint of the phase II portion of the trial is the overall response proportion (ORR) as assessed by RECIST 1.1. Secondary endpoints are safety/ toxicity, overall survival and PFS at 2 years. Planned accrual is 23 evaluable subjects over 2 years. Whole blood and serum will be analyzed for circulating immune cell repertoire and baseline tumor tissue will be sequenced.

Clinical trial identification: NCT02989714

Legal entity responsible for the study: Ajia Alva
Funding: Prometheus, University of Michigan

Disclosure: A. Alva: Advisory role for Eisai, AstraZeneca and Roche. Received research funding: Genentech, Novartis, Bristol-Myers Squib, BIND Bioscience, Acerta Pharma, Merck, Prometheus Laboratories, Covance, Mirati Therapeutics, United Biosources Corporation, ARIAD, Pfizer & Bayer. All other authors have declared no conflicts of interest.

Trial design: In an open-label, single-arm, single-center, phase 2 trial, patients (pts) with clinical stage N2-3 (TNM 2009, locally-advanced [LA]) or M1 PSCC will receive Cabo, orally, at a dose of 60 mg/day continuously until surgery, evidence of disease progression or onset of unacceptable toxicity. Prior ChT administration is not allowed. Response will be evaluated by RECIST criteria v.1.1, matched with 18FDG-PET/CT assessment, every 2 months. At each time of disease restaging, responding pts with LA PSCC who will be considered eligible to radical lymphadenectomy will undergo surgery. After surgery, pts will be managed according to standard guidelines. The primary endpoint (EP) is the objective response-rate (ORR=CR+PR according to RECIST v1.1). Secondary EP are safety, progression-free survival (PFS) and overall survival (OS), and pathologic response. The study is planned according to Simon’s Optimal two-stage design, with $H_1=20\%$ and $H_0=5\%$, and type I and type II error rates set at the 10% level. In stage 1, 12 evaluable pts will be accrued. If 1 pt at least will be responding, enrolment will be extended to the 2nd stage for further 25 pts. If, out of the total of 37 pts, 4 at least will be responding, treatment will be declared worthy for further investigations. Stopping rules based on the Bayesian posterior probability (PP) to demonstrate that the ORR exceeded 20% are set. Translational analyses on pre- and post-Cabo tumor samples and matched blood samples will include in-situ hybridization for HPV and next generation sequencing (Ion Torrent Personal Genome Machine). These profiles will be associated with response to treatment and PFS/OS (EudraCT number 2017-001963-19).

Clinical trial identification: EudraCT number 2017-001963-19

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale dei Tumori

Funding: Ipsen

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Cabozantinib in patients with advanced penile squamous cell carcinoma (PSCC): the open-label, single-arm, single-center, phase 2, CaboPen trial

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Background: Chemotherapy (ChT) exerts moderate activity in advanced and metastatic PSCC, and efficacy outcomes are poor. Neoadjuvant treatment is a reliable setting to address activity of new drug approach (Necchi A et al. ASCO-GU 2017). The vascular endothelial growth factor (VEGF) receptor is overexpressed in approximately 50% of PSCC. Cabozantinib (Cabo) is a multiple receptor tyrosine kinase inhibitor (TKI) primarily targeting MET and VEGFR2.
**Gynaecological Cancers**

Quality of life in patients with recurrent ovarian cancer (OC) treated with niraparib: Results from the ENGOT-OV16/NOVA Trial

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**Background:** The highly selective poly(ADP-ribose) polymerase (PARP) 1/2 inhibitor niraparib (ZEJULATM) concentrated in the tumor vs plasma in preclinical studies, delivering a disutility analysis of hematologic adverse events was conducted at different time points.

**Methods:** A mixed-effects growth-curve model adjusted for baseline demographic values and 3 stratification factors was constructed to model the relationship between treatment and PRO score for each measure. The relationship between health status and PROs was evaluated through a cross-sectional analysis of adjusted EQ-5D-5L health utility index (HUI) scores. A disparity analysis of hematologic adverse events was conducted at different time points.

**Results:** No significant difference in mean PRO scores was observed between niraparib and placebo arms in either cohort. Adjusted HUI scores were similar in both arms at baseline, but average adjusted HUI pre-progression scores trended higher in the niraparib arm (0.812 vs 0.803 in gBRCA mut cohort; 0.845 vs 0.828 in non-gBRCA mut cohort).

**Conclusion:** These data suggest pts with recurrent OC treated with niraparib following CR or PR to PBC can continuously maintain their QoL while on treatment.

Clinical trial identification: NCT01845724

Legal entity responsible for the study: TESARO, Inc.

Funding: TESARO, Inc.


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Pfizer, Sanofi, Taiho a.o. M. Johnson: Lilly Serono Kadmon Janssen Mirati Johnson: Lilly Serono Kadmon Janssen Mirati

Conclusions: In SOLO2, olaparib maintenance monotherapy improved PFS in pts with PSROC irrespective of the number of prior lines of PBC received.

Clinical trial identification: NCT01874353, 1 June 2017

Legal entity responsible for the study: AstraZeneca

Funding: AstraZeneca


The exposure-response relationship of niraparib in patients with gBRCAmut and non-gBRCAmut: Results from the ENGOT-OV16/NOVA Trial


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Background: Niraparib (ZEJULATM) is a selective PARP1/2 inhibitor approved for maintenance treatment of adults with recurrent ovarian cancer who are in a complete or partial response to platinum-based chemotherapy. In preclinical studies, niraparib concentrates in the tumor versus plasma, delivering >90% durable PARP1/2 inhibition and a persistent antitumor effect. We report the relationship between exposure and response of niraparib in patients (pts) enrolled in the ENGOT-OV16/NOVA trial.

Methods: Preliminary modeling for niraparib was performed using Phase 1 study data (N = 104) to identify the initial parameters for the pharmacokinetic model, which was further developed using combined Phase 1 and Phase 3 data (N = 512 pts) and the first-order conditional estimation with interaction method within NONMEM. Exposure-efficacy relationships were evaluated in the gBRCAmut and non-gBRCAmut cohorts separately.

Table 932PD: PFS subgroup analysis by number of prior lines of PBC received

<table>
<thead>
<tr>
<th>Prior lines of PBC received</th>
<th>Olaparib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=</td>
<td>110</td>
<td>62</td>
</tr>
<tr>
<td>PFS events, n (%)</td>
<td>57 (5.8)</td>
<td>44 (7.0)</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>22.1</td>
<td>5.7</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.38 (0.26–0.57)</td>
<td></td>
</tr>
</tbody>
</table>

n= Number of prior lines of PBC was unknown for one olaparib-arm patient

Progression or death by modified RECIST v1.1

*932PD Efficacy of olaparib maintenance therapy in patients (pts) with platinum-sensitive relapsed ovarian cancer (PSROC) by lines of prior chemotherapy Phase III SOLO2 trial (ENGOT-OV-21)


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Background: In the Phase III SOLO2 trial (NCT01874353), maintenance treatment with the poly(ADP-ribose) polymerase inhibitor olaparib (Lynparza) was shown to significantly improve progression-free survival (PFS) vs placebo in pts with PSROC and a BRCA1/2 mutation (HR 0.30, 95% CI 0.22–0.41; P < 0.0001; median 19.1 vs 5.5 months, Pujade-Lauraine et al NGO 2017). A previous retrospective analysis of data pooled from 6 studies of olaparib in pts with a germline BRCA1/2 mutation suggested that olaparib activity declined as the number of prior lines of chemotherapy received increased (Matulonis et al Ann Onc 2016). We report an analysis of PFS in SOLO2, grouped by number of prior lines of platinum-based chemotherapy (PBC) received by pts, performed to identify the most appropriate use of olaparib in the maintenance setting.

Methods: SOLO2 enrolled pts who had received 2 prior lines of PBC before being in response to their most recent regimen. Pts were randomized 1:1 to receive olaparib tablets (300 mg bid) or placebo. PFS was investigator assessed with modified RECIST v1.1. For the PFS subgroup analyses, subgroups were predefined; HRs were calculated using a Cox proportional hazards model.

Results: Of 295 randomized pts, 195 received olaparib and 99 received placebo. 85 pts in the olaparib arm (43.4%) had received 3 prior lines vs 57 pts (37.4%) in the placebo arm. Pts who had received 2 prior lines of PBC were more likely to have a platinum-free interval of > 12 months (70.9% vs 48.3% and 40.0% for 3 and 4 or > 24 prior lines, respectively in the olaparib arm: 69.4% vs 60.8% and 23.5% placebo) and a complete response at baseline (50.9% vs 36.7% and 48.0% olaparib; 54.8% vs 35.0% and 35.3% placebo) vs pts who had received > 3 prior lines.
the efficacy was compared in pts with high exposure (> median exposure) vs low exposure (< median exposure). Maximum plasma concentration (C_max) and area under the curve over the dosing interval (AUC0-INF) at steady state (SS) were the exposure metrics. Prognosis-free survival (PFS) was used as efficacy endpoint. Hazard ratios (HR) and 95% confidence intervals (CI) for the low and high niraparib exposure groups in each cohort were provided, with exposure group as the independent variable and PFS as the dependent variable. Exposure and safety data of gBRCAmut and non-gBRCAmut cohorts were combined to evaluate exposure-safety relationships using logistic regression.

Results: In the gBRCAmut cohort, the HR was 0.91 (95% CI: 0.54-1.52) for niraparib exposure as measured by the SS AUC0, for pts in the high exposure vs. the low exposure group. In the gBRCAmut cohort, the HR was 0.70 (95% CI: 0.40-0.99). Logistic regression analysis did not show any significant relationship between the incidence of thrombocytopenia or anemia Grade ≥ 3 and the SS gemcitabine or AUC increase. Conclusions: Observed exposure-response relationships support the selection of 300 mg as the starting dose in both gBRCAmut and non-gBRCAmut pt populations. A trend towards increased efficacy associated with increased exposure was observed in the non-gBRCAmut cohort.

Clinical trial identification: NCT01847274

Legal entity responsible for the study: TESARO, Inc.

Funding: TESARO, Inc.


Funding:

Results: Efficacy of niraparib was comparable in pts < 65 y vs ≥ 65 y in both gBRCAmut and non-gBRCAmut cohorts (Table). Efficacy was also similar in pts < 70 y vs ≥ 70 y in both cohorts (gBRCAmut: < 70 y; HR = 0.30; ≥ 70 y; HR = 0.99. Non-gBRCAmut: < 70 y; HR = 0.47; ≥ 70 y; HR = 0.35), although the sample size of pts who ≥ 70 y in the gBRCAmut cohort was small (14 niraparib vs 7 placebo). The most common adverse events (AEs; nausea, constipation, fatigue, hypertension, anemia, thrombocytopenia, neutropenia) in the niraparib arm occurred with similar incidence in pts < 65 vs ≥ 65 y as well as in pts < 70 vs ≥ 70 y. Grade 3/4 AEs occurring in > 10% of niraparib-treated pts were consistent in pts < 65 y vs ≥ 65 y (thrombocytopenia, 27% vs 31%; anemia, 27% vs 20%; neutropenia, 12% vs 10%) and in pts < 70 y vs ≥ 70 y (thrombocytopenia, 28% vs 31%; anemia, 27% vs 13%; neutropenia, 11% vs 10%, respectively). There were no Grade 5 events.

Table: 934PD

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Patient Numbers</th>
<th>PFS Hazard Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niraparib</td>
<td>Placebo</td>
<td>gBRCAmut</td>
</tr>
<tr>
<td>&lt; 65 y</td>
<td>110</td>
<td>49</td>
</tr>
<tr>
<td>≥ 65 y</td>
<td>28</td>
<td>16</td>
</tr>
</tbody>
</table>

Conclusions: Niraparib was safe and highly effective in elderly patients.

Clinical trial identification: NCT01847274

Legal entity responsible for the study: TESARO, Inc.

Funding: None


935PD

**BRCA1&2 tumoral and germline status for ovarian cancer patients in first line setting within the PAOLA-01 trial**

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Background: PAOLA-01 is a randomized placebo-controlled, international phase III study, assessing olaparib in maintenance therapy in advanced high grade ovarian carcinoma patients responding to 1st line platinum-taxane-based chemotherapy plus bevacizumab. Stratification is performed on treatment outcome and on tumoral BRCA1/2
status (tBRCA) at screening. As secondary objective, the consistency between germline (gBRCA) and tBRCA testing is being explored.

**Methods:** This study is planned to recruit 762 pts in Europe and 24 in Japan. tBRCA status was assessed in 962 samples with a median turn around time of 40 days (range 8 - 260). Only 44 (4.6%) tumor samples were non-informative (too low tumor cellularity, 8 using capture method and 36 by resequencing respectively. A deleterious variant (DV) was reported in 279 (29%) samples (191 (68%) in BRCA1, 87 (31%) in BRCA2 and one in both genes). Twelve variants of unknown significance were identified for BRCA2 and 1 for BRCA1. For the 384 French pts, both gBRCA & tBRCA testing was performed in parallel we report the mutation rate detection in the Table below. Of note, only one large genomic rearrangement of BRCA1 was detected in blood sample exclusively.

**Conclusions:** tBRCA testing is a reliable tool for clinical trials with acceptable delay for clinical practice. Propportion of tBRCA testing failure is low and consistency with germline testing adequate for routine practice.

### Table: 935PD

<table>
<thead>
<tr>
<th>French Cohort</th>
<th>gBRCA + (%)</th>
<th>gBRCA- (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>tBRCA +</td>
<td>67 (17)</td>
<td>23 (6)</td>
<td>90 (24)</td>
</tr>
<tr>
<td>tBRCA -</td>
<td>1 (0.3)</td>
<td>270 (70)</td>
<td>271 (71)</td>
</tr>
<tr>
<td>Inconclusive tumor testing</td>
<td>1 (0.3)</td>
<td>22 (5.7)</td>
<td>23 (6)</td>
</tr>
<tr>
<td>total</td>
<td>69 (18)</td>
<td>315 (82)</td>
<td>384 (100)</td>
</tr>
</tbody>
</table>

**Clinical trial identification:** EudraCT: 2014-004027-52 NCT02477644 First received: June 18, 2017

**Legal entity responsible for the study:** ARCYCAG Research

**Funding:** AstraZeneca and Roche

**Disclosure:** I. Soubeyran: Fees from Astra-Zeneca, Roche and ThermoFisher, advisory boards fees from Astra-Zeneca, Pfizer and MSD for intervening expert. P. Harter: Consulting or advisory role; Roche, AstraZeneca, research funding. Astzeneca. A. Gonzoalez Martin: Consultant and speaker for Roche and Astra Zeneca. K. Fujwara: AstraZeneca as an advisory board, travel expense and research grant. Also has COI with Chugai-Roche for research grant. S. Pignata: Honoraria: Astra Zeneca, Roche, consultancy or advisory role: AstraZeneca, Roche; research funding. Roche. N. Colombo: Advisory Board: Roche and AstraZeneca; Out of this trial, advisory board: Tesaro, Clovis, Pharmamar, Advaxis, Pfizer. C. Marth: Honoraria: Roche, AstraZeneca, Pfizer; consultation or advisory role: Roche, AstraZeneca, Pfizer Travel, accommodations, expenses: Roche, AstraZeneca and Pfizer. I. Vergote: Consulting or advisory board: AstraZeneca. Z. I. Macipia: Consulting or advisory role: Roche, AMGEN, Sobi. AstraZeneca Travel, accommodations, expenses: SOK, Sobi, Roche, AstraZeneca. E. Pujade-Lauraine: Consulting or advisory role: Roche, AstraZeneca, Pfizer, speaker’s bureau; Roche, AstraZeneca, Pfizer; travel, accommodations, expenses: Roche, AstraZeneca, Pfizer. R. Ky-coq: Honoraria: Roche, Pfizer, Advaxis, Roche; consultation or advisory board. Roche, Pharmamar, AstraZeneca, Advaxis, travel, accommodations, expenses: Roche, Pharmamar, AstraZeneca. All other authors have declared no conflicts of interest.

**936PD**

**Actionable molecular alterations in advanced gynecologic malignancies: First results from the ProfiLER program (NCT01774409) in France**

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**Background:** Recent data suggest that programmed death ligand 1 (PD-L1) expression may predict response to anti-programmed death 1 (PD-1) therapy. This retrospective observational study evaluated the prognostic effect of PD-L1 expression in patients with histologically confirmed epithelial ovarian, primary peritoneal, or fallopian tube cancer (OCA).

**Methods:** Patients diagnosed with FIGO stages II-IV OCA from 2004-2012, at Aarhus University Hospital and Rigshospitalet, Copenhagen, Denmark, were included. PD-L1 expression was measured in tissue collected at OCA surgery, using immunohistochemistry with anti-PD-L1 22C3 antibody. PD-L1 expression was defined as: negative (<1% of tumor or inflammatory cells), minimally positive (1% - 5% of tumor cells), positive (5% - 40% of tumor cells), or high positive (>40% of tumor cells). Patients with negative PD-L1 expression were not considered platinum sensitive, whereas those refractory (TFI 4-6 mo) or resistant (TFI 6-12 mo) to platinum therapy were considered platinum sensitive, respectively.

**Results:** Median age of the 376 patients at diagnosis was 63 years (range, 26-86). 77% had histologic grade 2/3 serous adenocarcinoma, 46% had residual tumor after surgery, and 90%, 7%, and 1% had FIGO stages II, III, and IV disease, respectively. 55% were platinum-sensitive, 44% platinum-resistant, and platinum-refractory disease comprised 6% 27%, 15%, and 9% of patients, respectively. 50.5% of patients were PD-L1+ with prevalence increasing with increased platinum sensitivity (P for linear trend <0.05). Median overall survival (OS) was 43 mo (50.4 mo in PD-L1 vs 38.3 mo in PD-L1+ patients). A statistically significant association was seen between PD-L1+ tumors and longer OS (adjusted hazard ratio [aHR], 0.71 [95% CI, 0.55-0.91]). The association was not significant in platinum-insensitive patients (aHR, 0.82 [0.50-1.36]), but there was a tendency towards significance in platinum-sensitive patients (0.77 [0.57-0.91]), driven by those with a TFI of 6-12 mo.

**Conclusions:** PD-L1 was frequently expressed in advanced OCA patients, and expression may be prognostic, particularly in those with partial platinum-sensitive OCA.

**Legal entity responsible for the study:** Merck & Co., Inc.

**Funding:** Merck & Co., Inc.

**Disclosure:** T.T. Vo: Employed by, own stock in, and have received research grants from Merck & Co., Inc., W. Zhou, M. Busch-Sørensen, D. Chappell. Employed by and own stock in Merck & Co., Inc. T. Steiniche: Received research funding from and have been reimbursed for travel and accommodation expenses by Merck & Co., Inc. All other authors have declared no conflicts of interest.
Background: little is known about the immune microenvironment of OCCC and its impact on outcomes. We studied the expression of a panel of immune response genes in OCCC to identify the presence and prognostic relevance of irGES in these tumours.

Methods: Immune response gene profiling was performed on 84 FFPE OCCC samples with matched clinical outcomes, collected between 2003 – 2016, using the nonstringent nCounter PanCancer Immune Profiling Panel. Unsupervised hierarchical clustering analysis was performed and each sample underwent analysis for protein levels of PD-1, PD-L1, MMIR and ARID1A via immunohistochemistry (IHC).

Results: Total of 74/84 samples were successfully profiled. Median age at diagnosis was 53 yrs. (41 - 65 yrs) were stage 1 (7.9%) stage 2, 2/4. (32.4%) stage 3, 2. (2.7%) stage 4 6/47 (8.6%) of pts received adjuvant chemotherapy post Surgery with 38% recurrence rate (median PFS 27 months (m)). Median follow up was 36m. Based on irGES, pts were classified as high-risk or low-risk. High-risk was defined by high risk score and low risk by low risk score.

Conclusions: OCCC are heterogeneous and can be classified into 4 molecular subgroups based on their irGES profiles with distinct clinicopathological characteristics and prognostic outcomes. If validated in larger datasets, these signatures may serve to inform clinical trial design.

Legal entity responsible for the study: Institute Review Board Singapore

Funding: None

Disclosure: All authors have declared no conflicts of interest.

938PD
An increased ratio of cytotoxic to suppressive T cells after neoadjuvant chemotherapy (NACT) is prognostic in advanced ovarian cancer

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Background: At diagnosis, tumor-infiltrating lymphocytes (TILs) are prognostic in epithelial ovarian cancer (EOC). We recently demonstrated that neoadjuvant chemortherapy (NACT) significantly increased stromal TILs and stromal TILs remained prognostically significant after NACT. Here, we investigated the impact of NACT on different immune subpopulations and their relationship with clinical outcome.

Methods: Tissue microarrays of EOC (145 pre-NACT, 139 post-NACT, including 83 matched samples) were analyzed for CD3+ , CD8+ and FOXP3+ by immunohistochemistry. Stromal TILs scored as percentage of stromal area, intraepithelial TILs as ratio post-NACT. Stromal TILs were correlated with age, grade, tumor size, histology, number of LN, BRCA mutation status and outcomes of the cohort. The association between TILs and clinicopathological parameters was analyzed using the Chi-square test.

Results: NACT significantly increased stromal CD3+ (+p = 0.005) and CD8+ (+p = 0.009) and intraepithelial CD8+ (+p = 0.02) in matched samples and remained significant among paired samples for stromal CD3+ and CD8+ (+p = 0.03 and p = 0.009). Neither CD3+ nor CD8+ expression correlated with outcome at diagnosis or post-NACT, however reduced accumulation of FOXP3+ post-NACT (<5%) was significantly associated with improved PFS (HR = 0.99; p = 0.016). A high stromal CD8+ / FOXP3+ ratio post-NACT strongly correlated with improved PFS (median 90 vs 188.5 months; p = 0.0001) and OS (median 30.70 vs 37.10 months; p = 0.0029). In contrast, at diagnosis, CD8+/FOXP3+ was not associated with prognosis.

Conclusions: NACT has a significant impact on the balance of cytotoxic versus suppressive T cells and a high ratio of CD8+/FOXP3+ post-NACT was most significantly associated with improved PFS and OS. Whether this could select patients for immune therapies in the post-operative setting should be investigated.

Legal entity responsible for the study: Institut Gustave Roussy

Funding: INCA and MEUR

Disclosure: All authors have declared no conflicts of interest.

939PD
Long term quality of life among epithelial ovarian cancer patients: The GINECO case/control VIROVIAYA Study


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Background: If epithelial ovarian cancer (EOC) had a poor prognosis, more than 20% of patients (pts) can expect long remission. Few data are available on long term quality of life (QoL) in these pts and results reported were usually not compared to those of healthy controls.

VIROVIAYA was a large national case-control study comparing pts reported outcomes (PQOs) among EOC pts without relapse within 3 years after first line treatment and a group of healthy women.

Methods: Pts were recruited in 27 French centers and clinical characteristics were issued from medical charts. Controls were randomized from electoral lists. Pts and controls matched on age. They filled in a form including PQOs questionnaires: QoL, neurotoxicity and fatigue (FACT/G, FACT/O, FACT/GOG-Ntx, FACT/P), anxiety and depression (HADS), sleep disturbance (ISI) and Physical activity (IPAQ).

Results: 318 pairs were analysed (from 349 pts and 327 controls included). Median age: 65 (20-86), high level of education: 52% and 58%, respectively. Pts characteristics: FIGO stage I/II (49%), III/IV (47%) unknown (4%); major histology, serous (50%), endometrioid (16%); clear cells (8%), mucinous (4%); BRCA1/2 mutations (n = 21); 15%, unknown (n = 168). 99% of the pts had a surgery and 96% received platinum based chemotherapy, associated with antiangiogenic agent (14%) Interval from first line therapy: median 5 years (210-24). Pts reported lower physical and functional QOL scores (p = 0.03 and p = 0.0002), higher score of fatigue (p < 0.0001), and poorer quality of sleep (p = 0.0001) than controls. No difference of scores of anxiety and depression was observed between the 2 groups. TOS score (related to ovaries, cancer and treatment) and score of neurotoxicity were higher among patients (p = 0.0001); 26% of pts reported severe fatigue, more than 70% of the pts were concerned about digestive symptoms and severe neurotoxicity. Only 18% of the pts and controls had an active physical activity.

Conclusions: Compared to healthy women, EOC pts presented poorer long term QoL, fatigue with important neurotoxicity and digestive symptoms. Physicians have to take in count the late effects of treatments to help the pts to cope with the sequelae.

Legal entity responsible for the study: Centre Francois Baclesse

Funding: Fondation de France; Ligue Nationale Contre Le Cancer

Disclosure: All authors have declared no conflicts of interest.

941PD
An investigator initiated, open label, randomized, controlled, multicentric study, to assess the safety and efficacy of nimotuzumab (BIOMAb-EGFR) concurrent with cisplatin and radiotherapy (RT) in histologically documented squamous cell carcinoma of the cervix


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Background: EGFR inhibitors have proven to improve the efficacy of anticancer treatments in lung, colon, pancreas, or HNC. Results from studies show EGFR expression in cervical Ca to improve survival outcomes in the same. This study was designed to assess...
safety and efficacy of Nimotuzumab with concurrent cisplatin and RT in patients with Ca Cervix.

Methods: In this open-label randomized controlled multicentric study 100 patients with histologically confirmed Ca Cervix were recruited over a 4 year period with an equal allocation of 1:1 for intervention (Standard arm vs concurrent CTET (Cisplatin 40mg/m² weekly IV + RT) vs 200mg weekly BIOMAB IV (n = 50) on same day of cis-platin infusion) vs. standard arm only (n = 50). At 2 years data were available for 39 patients in the intervention arm and 35 patients in standard arm. The size of the lesion was documented using CT/PECT at baseline. The response was analyzed using RECIST criteria at the following treatment every 3 months for subsequent 2 years. Toxicity was assessed using CTCAE v4 toxicity criteria.

Results: There were 74 evaluable patients at end of 2 years. The mean age was 49±6.10.2 years. The complete response following treatment was seen in 37.8% (BIOMAB arm) of patients at two years following treatment compared to 38.2% in standard arm. However, progressive disease was seen more in standard arm (52.9%) compared to BIOMAB arm (35.1%). Best overall response was seen in 64.9% patients in the intervention arm compared to 47.1% patients in the standard arm at two years following treatment which is significant. At 2 years 60% progressed on standard arm compared to 37.8% in the intervention arm. The mean estimate of progression-free survival being 36 months vs. 56.5 months (BioMab arm) (Log rank Mantel–Cox x²= 3.9, p < 0.05).

Except for one patient with biomab sensitivity, there was no additional toxicity compared to the standard arm.

Conclusions: Nimotuzumab appears to be safe and effective targeted therapy in cervical cancer patients with long-term benefits.

Clinical trial identification: TS-01-2009

Legal entity responsible for the study: Healthcare Global Enterprises Ltd.

Funding: BIOCON

Disclosure: All authors have declared no conflicts of interest.

943P Location of mutation in BRCA2 gene and survival in patients with ovarian cancer

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Background: BRCA2 plays a central role in homologous recombination through loading RAD51 on DNA double strand breaks. Among ovarian cancer (OC) patients, carriers of BRCA2 mutations have better survival than BRCA1 carriers and non-carriers. The objective of this study is to determine whether location of mutations in BRCA2 gene impacts survival of OC patients.

Methods: A study cohort of 540 women with OC, who underwent genetic testing for BRCA1 and BRCA2 genes and received platinum-based chemotherapy, were identified in four hospitals in Switzerland and France. Duration of follow-up was 4.14 years. The Cancer Genome Atlas (TCGA) cohort of high-grade serous ovarian carcinomas (n = 316) was used as a validation cohort. Progression-free survival (PFS) and overall survival (OS) were analyzed.

Results: In the study cohort, 74 and 78 patients were carriers of germline mutations of BRCA1 and BRCA2, respectively. After adjustment for FIGO stage and macroscopic residual disease, BRCA2 carriers harboring truncating mutations in the RAD51 binding domain (RAD51-BD; exon 11) have significantly prolonged 5-years PFS (58%; adjusted Hazard ratio [HR: 0.36, 95% CI: 0.20-0.64; p<0.001) compared to non-carriers. BRCA2 carriers with mutations located in other domains of the gene have not prolonged 5-years PFS (28%; adjusted HR, 0.67; 95% CI, 0.42-1.07; p=0.094). In the TCGA cohort, after adjustment for FIGO stage and macroscopic residual disease, only BRCA2 carriers harboring germline or somatic mutations in the RAD51-BD had prolonged 5-years PFS (46%; adjusted HR, 0.30; 95% CI, 0.13-0.68; p<0.004) and 5-years OS (78%; adjusted HR, 0.99; 95% CI, 0.02-0.38; p<0.001), compared to non-carriers.

Conclusions: Among patients with ovarian cancer, BRCA2 carriers having mutations located to the RAD51-BD have prolonged progression-free survival and overall survival. Legal entity responsible for the study: S. Istitubar Labidi-Galy

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Disclosure: All authors have declared no conflicts of interest.

944P POLE mutations and MSI were positive predictive factors for progression free survival in endometrial cancer patients at the risk of recurrence

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Background: The Cancer Genome Atlas (TCGA) reported the genomic subgroups of endometrial cancer (EC); POLE mutation, Microsatellite instability (MSI), copy number low, and copy number high. Cancer with POLE mutation or MSI indicates hyper or high mutated, and they are considered to have some potential for good prognosis through immunoactivtivity in tumor microenvironment. In this study, we investigated the POLE mutation and MSI status in EC, and the correlation between the subtypes and prognosis and considered about the necessity of adjuvant therapy to good prognostic group.

Methods: In this study, we extracted tumor DNA from formalin-fixed, paraffin-embbeded tissue of 325 EC tissues surgically resected at Okayama University

Exelixis, Lilly, Morphophet, Pronova, Roche, Advisory Boards and/or Board of Directors for Roche, Genentech and multiple other pharmaceutical companies exceeding the character limit and thus not listed here. J. Ray-Coquard. Advisory Board for Roche. A. Leary. Advisory board and/or board of directors for AstaZenza, Clavis, GamaMabs, Research funding: GamaMabs, Merus. A. Lahr, I. Frankovic, S. Rossomanno, A. Sahbi, K. Longauer: Employment Roche. P. Gerber, F. Heil, C. Boetsch, O. Krieter: Stock options and employment Roche. T. Nayak: Stock options. All other authors have declared no conflicts of interest.
Background: In recent years there has been increasing interest in the study of circulating tumor cells (CTC) and plasma cell-free circulating DNA (ctDNA) as a new biomarker in neoplastic diseases. Our work aims to clarify its clinical role in ovarian epithelial carcinoma (OEC).

Methods: A prospective, multicenter, observational study has been conducted for 3 years in patients with advanced or recurrent OEC. The predictive value and prognosis of CTC and ctDNA have been determined for both progression-free survival (PFS) and overall survival (OS). Their values have been compared with a control group. CTC were analyzed by the CellSearch method and ctDNA by ALU-sequences-based quantitative PCR using two primers (ALU115 and ALU247); ctDNA integrity was calculated by droplet digital PCR for PIK3CA or KRAS mutations. We defined ctDNA detection to be positive when the corresponding mutations were detected in plasma cell-free DNA.

Results: In 104 patients, 75, 25, and 4 had malignant, borderline, and benign ovarian tumors, respectively. The detection rates for ctDNA were 32% (24/75), 16% (4/25), and 0% (0/4) in patients with malignant, borderline, and benign ovarian tumors, respectively. PIK3CA and KRAS mutations in the plasma cell-free DNA were detected in 33.3% (11/33) and 30.2% (13/43) of patients with malignant ovarian tumors, respectively. We investigated the relationship between ctDNA detection and clinicopathological features in 73 epithelial ovarian cancer (EOC) patients. The detection rate of ctDNA was associated with advanced stage (p = 0.019) and positive peritoneal cytology (p = 0.011), but not with the histologic subtype or residual tumor status. In univariate analysis, ctDNA detection was associated with shorter progression-free survival in EOC patients (p < 0.001). Multivariate analysis revealed that the stage, residual tumors, and ctDNA were independently associated with an increased risk of recurrence.

Conclusions: ctDNA was detected in approximately 30% of EOC patients in this study regardless of histologic types or the genes examined. The presence of ctDNA in the blood is an independent prognostic factor for recurrence, which suggests potential tumor spread.

Legal entity responsible for the study: University Clinical Hospital Virgen Arrixaca - Murcia/ES

Funding: None

Disclosure: All authors have declared no conflicts of interest.

496P Predictive and prognostic value of tumor cells and circulating plasma free DNA in advanced epithelial ovarian carcinoma


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Background: In recent years there has been increasing interest in the study of circulating tumor cells (CTC) and plasma cell-free circulating DNA (ctDNA) as a new biomarker in neoplastic diseases. Our work aims to clarify its clinical role in ovarian epithelial carcinoma (OEC).

Methods: A prospective, multicenter, observational study has been conducted for 3 years in patients with advanced or recurrent OEC. The predictive value and prognosis of CTC and ctDNA have been determined for both progression-free survival (PFS) and overall survival (OS). Their values have been compared with a control group. CTC were analyzed by the CellSearch method and ctDNA by ALU-sequences-based quantitative PCR using two primers (ALU115 and ALU247); ctDNA integrity was calculated by droplet digital PCR for PIK3CA or KRAS mutations. We defined ctDNA detection to be positive when the corresponding mutations were detected in plasma cell-free DNA.

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Conclusions: ctDNA was detected in approximately 30% of EOC patients in this study regardless of histologic types or the genes examined. The presence of ctDNA in the blood is an independent prognostic factor for recurrence, which suggests potential tumor spread.

Legal entity responsible for the study: University Clinical Hospital Virgen Arrixaca - Murcia/ES

Funding: None

Disclosure: All authors have declared no conflicts of interest.
debunking surgery (IDS) rate, complete resection rate and progression-free survival (PFS), and explored their potential predictive impact on ORR and PFS according to bevacizumab therapy.

Results: In 68 pts with an available CTC count at baseline, CTC+ pts (n = 29) had a 75.9% ORR (at IDS), vs 59.3% for pts with 0 CTC (n = 59); ORR = 2.2 (0.8-5.8) (OR-adj=1.8 [0.8-5.8]). Respectively, 58.6% vs 66.1% were aminable to IDS and 55.2% vs 54.2% achieved a complete resection. Median PFS was 21 m [15.0-25.4] in CTC+ pts and 25.8 m [18.5-27.2] in pts with 0 CTC (HR = 1.5 [0.8-2.8] and HR-adj=1.7 [0.9-3.2]). CTC counts at IDS were available in 70 pts. At IDS, a complete resection was achieved in 66.7% of CTC+ pts (n = 6), and in 68.8% of pts with 0 CTC (n = 64).

Exploration of the potential predictive impact of CTC is described in the table.

**Table: 947P**

<table>
<thead>
<tr>
<th>Prognostic approach</th>
<th>CTC+ at baseline (n = 29)</th>
<th>CTC- at baseline (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR at IDS</td>
<td>75.9%</td>
<td>59.3%</td>
</tr>
<tr>
<td>Median PFS [95% CI]</td>
<td>75.9 [21.0 m [15.0-25.4]</td>
<td>59.3 [25.8 m [18.5-27.2]</td>
</tr>
<tr>
<td>Predictive approach</td>
<td>Beva (n = 36)</td>
<td>56.5%</td>
</tr>
<tr>
<td>CP (n = 23)</td>
<td>20.3 [13.8-27.2]</td>
<td>56.5%</td>
</tr>
<tr>
<td>ORR at IDS</td>
<td>82.4%</td>
<td></td>
</tr>
<tr>
<td>Median PFS [95% CI]</td>
<td>67.7%</td>
<td></td>
</tr>
<tr>
<td>Predictive approach</td>
<td>Beva (n = 17)</td>
<td>52.9%</td>
</tr>
<tr>
<td>CP (n = 12)</td>
<td>20.6 [8.0-25.4]</td>
<td>83.3%</td>
</tr>
</tbody>
</table>

**Conclusions:** Baseline CTC counts in OC patients receiving neoadjuvant chemotherapy +/- bevacizumab carry dual prognostic information: CTC count at IDS do not add any information, CTC+ seems to be associated with a higher ORR, while 0 CTC count seems to be a prognostic factor with better PFS, in the whole population and among patients treated with bevacizumab.

**Clinical trial identification:** 2012-01144-22

Legal entity responsible for the study: Roche

**Funding: Roche**

**Disclosure:** T. de La Motte Rouge: Consultancy work: AstraZeneca, Roche, MSD, Eisai, Sanofi
SanoT Travel grants/meeting support: Roche, Novartis, Pfizer.
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**Background:** Close proximity between cytotoxic T cells and tumor cells is key to effective immunotherapy. Ovarian cancer exhibits diverse immune phenotypes with distinct prevalence and spatial localization of CD8+ T cells. This study is aimed to characterize the molecular mechanisms orchestrating the localization and function of CD8+ T Cells in ovarian cancer.

**Methods:** CD8 IHC and RNAseq were performed on 277 ovarian tumor tissues from ICON7 phase 3 trial. CD8 T-cells in tumor vs. stromal area was assessed by digital pathology. A Random Forest regression model was constructed to identify molecular features associated with enumeration or spatial localization of CD8+ T cells. In situ validation was performed by MHCI IHC and FAP RNAish. Functional role of ovarian fibroblasts was characterized by ex vivo T cell function assays.

**Results:** We identified three main immune phenotypes, including T-cell infiltrated, T-cell excluded, and immune deserts. The immune phenotypes are highly associated with prognostic and the molecular subtypes of ovarian cancer. The T-cell infiltrated phenotype is denoted by high expression of T-effector signatures and antigen presentation machinery. The T-cell excluded phenotype showed similar expression of T-effector signatures as the T-cell infiltrated phenotype, however, most of the CD8+ T-cells were excluded from the tumor bed. The T-cell excluded phenotype showed high expression of the reactive stroma signatures (i.e., FAP), and low expression of class I antigen presentation genes. Lastly, the immune deserts present phenotype featured low prevalence of CD8+ T-cells, and high expression of neuroendocrine and metabolic pathways. In situ analysis confirmed the two key molecular features associated with the T-cell excluded phenotype: 1) loss of the MHCI expression in the tumor compartment, and 2) high FAP expression in CAFs. Co-culturing of ovarian fibroblasts with T-cells resulted in reduced T-cell activation and proliferation.

**Conclusions:** Our study uncovered key molecular mechanisms mediating the interplay between CD8+ T-cell localization and function in ovarian cancer. Our findings underscore the potential of targeting reactive stroma as a novel therapeutic strategy to optimize immunotherapy for ovarian cancer patients.

Legal entity responsible for the study: Genentech

**Funding:** Genentech


**948P**

**Genomic instability is associated with increased immune infiltration and PD-L1 expression in epithelial ovarian cancer**


**Background:** High mutation load secondary to mutagenic exposures such as smoking or to mutations in mismatch DNA repair genes has been associated with increased tumor immune infiltration and response to immune therapies. Ovarian cancers (OC) demonstrate low mutation load, but high degree of genomic instability (GI) attributable to frequent defects in the homologous recombination DNA repair pathway. We sought to investigate whether GI predicted increased infiltration by tumor infiltrating lymphocytes (TILs) and PD-L1 expression in OC.

**Methods:** TILs were evaluated on FFPE OC samples and scored as percentage of stromal area. PDL1 expression was quantified as percent positive immune cells. GI was measured as the number of copy number alterations >15Mb by Oncoscan SNParray on DNA from the same FFPE samples and high GI score (GIS) defined as > median. Correlations were evaluated using a Spearman rank and differences by Mann-Whitney.

**Results:** 66 tumor samples were evaluable for both GIS and immune infiltration. GIS and TILs showed significant variability ranging from 0 to 64 (median=28) and from 5 to 90% (median=20%) for GIS and TILs, respectively. GIS was significantly higher among high grade serous or endometrioid OC than among low grade tumors (GIS=29.5 vs 5; p < 0.001) and non-significantly greater among patients with BRCA mutations and/or family history compared to wild-type OC with no family history (p = 0.12). GIS and TILs were highly correlated (R = 0.4; p = 0.0019) and median TILs were significantly increased in GIS-high vs low tumors (29% vs 19%; p = 0.0028). Fig 1) as was immune cell PD-L1 expression (p = 0.025). Fig 1 Increased TILs in tumors with high genomic instability.
Conclusions: High genomic instability correlated with increased tumor infiltrating lymphocytes and PDL1 expression. Whether CIS could provide a simple and predictive biomarker for immune therapies in OC should be investigated.

Legal entity responsible for the study: LEARY Alexandra

Funding: INCa (Institut national du cancer)

Disclosure: All authors have declared no conflicts of interest.

949P

Tumor microenvironment in high serous ovarian cancer: Characterization of the infiltration pattern and analysis of its prognostic value

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Background: Lymphocytic infiltration areas (immunoactive) are frequently found in ovarian cancer, which is associated with a better prognosis and increased survival. Therefore, the study of different patterns and degree of infiltration would help us to better understand the relationship between immune and tumor cells and its prognostic implications.

Methods: This retrospective study includes samples from 57 patients with high grade serous ovarian cancer (HGSOc) who underwent cytoreductive surgery. The pattern of infiltration, localization and degree of lymphocyte infiltration in the tumor was evaluated. A set of clinical variables such as smoking, age, type of surgery, intention of treatment, type of response, as well as lymphocytic infiltration were evaluated to assess prognosis.

Results: In our cohort, the median age was 61.5 years, there were 60% of smokers, and most of the cases were FIGO stages III and IV (15.3%, stage I, 8.5% stage II, 54.3% stage III and 22% stage IV). As expected, patients over 65 years, as well as the group of more advanced stages (III and IV) showed a shorter overall survival (OS, 30.17 vs 99.90 months, p = 0.009, 38.73 months vs NR, p = 0.005, respectively). Smoking status was also analyzed but no significant effect on survival was found (OS, p = 0.993).

Interestingly, patients with an intratumoral lymphocytic infiltrate had a better prognosis compared to the group that had only a peritumoral pattern (OS, 44.57 months vs NR, p = 0.041). In addition, those with a diffuse infiltration pattern presented a better prognosis compared to those with a focal pattern (OS, 20.20 months vs NR p = 0.003).

Finally, a tendency for a better OS was seen for those patients with a strong degree of infiltration in the tumor.

Conclusions: HGSOC represents a group of highly immunoreactive tumors. Those with the best prognosis are represented by an intratumoral, diffuse pattern with a strong degree of infiltration, these findings could open a new window for therapeutic approaches in HGSOc.

Legal entity responsible for the study: Fundación de Investigación Hospital General de Valencia

Funding: None

Disclosure: All authors have declared no conflicts of interest.

950P

Gene mutational analyses in 154 ovarian cancer (OC) samples from the ROSIA study of front-line bevacizumab (BEV)-containing therapy for OC

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Background: In the single-arm ROSIA study (NCT01239732), 1021 patients (pts) with newly diagnosed OC received 12–24 wks of carboplatin + paclitaxel with BEV for up to 24 mo or until progression [Oza 2016]. Progression-free survival (PFS) was a secondary endpoint.

Methods: In an optional translational research study, tumor tissue samples collected before BEV were analysed using Foundation Medicine Inc.’s FoundationOne® (FMOne) gene panel. Prevalence of gene alterations, tumour mutational burden (TMB) and potential prognostic effects were assessed in exploratory gene mutational analysis using Cox proportional hazards models. Correlations between TMB and BRCA1 mutation and immunohistochemical expression of the immune markers PD-L1 and CD8 were assessed.

Results: The FMOne population (n = 154) was representative of the ITT population (n = 1021) for baseline characteristics but had slightly more favourable PES (median 30.2 vs 25.5 mo, respectively; hazard ratio [HR] 1.16 [95% CI 0.92–1.45]; p = 0.21). The most common gene alterations (predominantly short variant) were TP53 (79% of pts), BRCA1 (22%), NF1 (14%), KRAS (10%), P53CA (9%) and BRCA2 (7%). MTRC, GNAS and CCNE1 were amplified in 25%, 16%, 7% and 7%, respectively. The mean TMB (excluding germline polymorphisms and known cancer drivers) was 4.3/ Mbase (M base range 0–43). Only 2 pts had a TMB >15/Mb; 13 had a TMB ≥5/Mb.

In univariate Cox regression analyses, none of the mutations explored showed a clear association with PFS. PFS slightly (not statistically significantly) favoured pts with (n = 34) vs without (n = 110) BRCA1 mutation (median 30.4 vs 28.1 mo, respectively; HR 0.76 [95% CI 0.44–1.31]; p = 0.32). TMB and PFS showed no association.

No meaningful correlations were seen between either TMB or BRCA1 mutation and expression of the immune markers PD-L1 and CD8 on immune cells.

Conclusions: Samples from pts with newly diagnosed OC indicated relatively infrequent gene alterations and low TMB. None of the gene alterations evaluated suggested prognostic value, but low frequency of these mutations and the relatively small number of samples in ROSIA interpretation, particularly for the correlation analyses.

Clinical trial identification: NCT01239732

Legal entity responsible for the study: F Hoffmann-La Roche Ltd

Funding: F Hoffmann-La Roche Ltd


Travel expenses from Roche for advisory boards and ROSIA steering committee meetings. All other authors have declared no conflicts of interest.

951P

A retrospective study of endocrine therapy in high grade serous ovarian carcinoma

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Background: The degree of oestrogen receptor (ER) expression in ovarian cancer correlates well with its endocrine sensitivity. However, the use of endocrine therapy (ET) in relapsed disease is variable in part due to the lack of phase III data. It is thus under-licensed and not a standard of care. Here we describe the endocrine sensitivity of high grade serous ovarian carcinoma (HGSOc) in a large retrospective cohort.

Methods: Patients were eligible if they had HGSOc treated with prior chemotherapy, and received at least 4 weeks of ET. Exclusion criteria included: ET as a maintenance treatment and unknown duration of therapy (DOT). The best CA125 response across the DOT was recorded as per modified GCIG criteria. Stable CA125 responses had to be maintained for at least 12 weeks. The primary endpoint was DOT. Secondary endpoints

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were time to next therapy (TTNT) from treatment initiation, CA125 objective response rate (ORR) and clinical benefit rate (CBR).

Results: 593 patients were identified from the Edinburgh Ovarian Cancer Database between January 1974 and December 2015. 267 patients met the eligibility criteria (78.3% letrozole, 19.3% tamoxifen, 2.2% megestrol acetate). Median DOT and TTNT were 122.5 days (range 28-1427 days) and 161 days (range 41-2345 days), respectively. 33.2% and 14.6% of patients received ET for > 180 and > 365 days, respectively. Of 38 patients on ET for > 365 days, 29 (76%) received ET as 2nd line therapy, 9 (24%) as 3rd line therapy and none as 4th line later. The CA125 ORR and CBRA in evaluable pts was 11.4% (2017) and 48.6% (85175), respectively. The CA125 CBR, median DOT and TTNT between different ER histo-score ranges are compared in Table. In early (2nd line) vs late (3rd line onwards) use of ET, the median DOT and TTNT was 140 vs 98 days (HR = 0.68 [95% CI 0.53-0.87]) and 167 vs 138 days (p = 0.022), respectively.

Conclusions: The endocrine sensitivity of HGSOC is significantly influenced by the degree of ER expression and line of treatment that ET is used. Early introduction of ET in the management of relapsed HGSOC should be considered particularly in tumours with an ER histo-score of ≥ 200.

Legal entity responsible for the study: Professor Charlie Gourley

Funding: None

Disclosure: M. MacKeam: For the last 10 years; Ad boards: Tesaro, Bristol-Myers Squibb, Roche, Boehringer Ingelheim, Eli Lilly and Glaxo Smith Kline. F. Nussey: Has been the local principle investigator for the SOLO 2 trial (randomised phase III trial of maintenance Olaparib in BRCA mutant patients). C. Gourley: AstraZeneca (advisory board, lecture fees, research funding); Clovis (advisory board); Tesaro (advisory board, lecture fees); Roche (advisory board); Novartis (research funding); Nucana (advisory board, research funding) and Aprea (research funding). All other authors have declared no conflicts of interest.

952P

Randomised prospective study of maintenance tamoxifen versus post adjuvant chemotherapy surveillance only in advanced ovarian cancer patients

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Background: Treatment of advanced ovarian cancer results in a high objective response rate (> 70% to 80%), but disease recurs in most patients. Some studies have been done to understand the role of maintenance therapy after conventional adjuvant chemotherapy. Maintenance therapy must balance prevention of disease recurrence with cumulative toxic effects and reduction in quality of life. The effects of maintenance therapy with chemotherapy (e.g. paclitaxel maintenance) or antiangiogenetic agents (e.g. bevacizumab or panpaprazib) have been studied, but results have been conflicting and without significant benefit in overall survival. We have performed this study to assess the role of maintenance tamoxifen post adjuvant chemotherapy in patients with advanced ovarian cancer.

Methods: In this prospective study, done in a tertiary care centre in northern India, patients with advanced ovarian cancer (stage III and IV), post conventional adjuvant chemotherapy, were randomly enrolled from Sep 2012 to April 2015. Tamoxifen maintenance was given at a dose of 20 mg twice a day for entire follow up period. The progression free survival (PFS) was analyzed.

Results: In total 100 patients were enrolled: 50 patients were given tamoxifen and 50 patients were put on post adjuvant treatment surveillance. The median age was 51.0 years (31-69 years). Median follow up of these patients was 14 months (6-22 months). Median increase in PFS was 6.3 months (95% CI 4.52-6.14 months) in patients treated with maintenance tamoxifen and there were no grade 3/4 side effects seen in this group.

Conclusions: Maintenance tamoxifen prolongs PFS by 6.3 months when compared to no treatment after conventional adjuvant chemotherapy. Further studies should be planned for comparison of maintenance tamoxifen with maintenance chemotherapy (e.g. paclitaxel maintenance) or antiangiogenetic agents.

Legal entity responsible for the study: Rajiv Gandhi Cancer Institute and Research Center

Funding: None

Disclosure: All authors have declared no conflicts of interest.

953P

A phase 1 study to evaluate the safety and tolerability of bevacizumab-niraparib combination therapy and determine the recommended phase 2 dose (RP2D) in women with platinum-sensitive epithelial ovarian cancer (ENGOT-OV24/AVANOVA1)


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Background: A phase 2 randomized study has indicated that the combination of a poly(ADP-ribose) polymerase inhibitor (PARPi) with an anti-angiogenic drug is superior to PARPi alone.

Methods: Bevacizumab 15 mg/kg IV q 21 days (fixed dose) was administered with escalating dose of niraparib capsules (100, 200, 300 mg daily) in a classic 3 + 3 escalation design. Platinum-sensitive ovarian cancer patients (pts) with high-grade serous/ endometrioid carcinoma and with measurable disease (RECIST or GCIG criteria) were eligible. The primary objective was to evaluate the safety and tolerability of the bevacizumab-niraparib combination therapy and determine the RP2D of bevacizumab-niraparib. 

Results: Twelve pts (3 + 3 + 6) were enrolled to three dose levels. Three of 12 pts had gBRCA2 mutation, while the others were non-gBRCAmt. During the first cycle, patients experienced hypertension (G3 = 5 pts), anemia (G3 = 3 pts), thrombocytopenia (G3 = 1 pt), fatigue (G2 = 1 pt), constipation (G2 = 1 pt), and nausea (G2 = 1 pt). One dose-limiting toxicity (Grade 3 thrombocytopenia that persisted for > 5 days) was observed at the highest dose level, and the RP2D is therefore bevacizumab 15 mg/kg with niraparib capsules 300 mg. Niraparib dose reductions occurred in four pts (cohort 2: 1 pt, cohort 3: 3 pts), and bevacizumab dose reduction occurred in two pts. Three pts are still on treatment, while nine pts have discontinued treatment (8 progressive disease; 1 withdrawal of consent). Disease control rate was 91%, and response rate was 49% (1 CR, 4 PR).

Niraparib pharmacokinetics were consistent with historical data. Overlapping exposure was observed across the dose range tested at both CID1 and CID2.

Conclusions: The bevacizumab-niraparib combination has hematologic dose-limiting toxicity and expected, manageable class toxicities with preliminary evidence of efficacy. The PK profiles of niraparib co-administered with bevacizumab are similar to historical data: A phase 2 randomized 2-arm trial is ongoing (AVANOVA2, NCT02354131).

Clinical trial identification: NCT02354131.

Legal entity responsible for the study: Nordic Society for Gynecologic Oncology

Funding: TESARO, Inc.

Disclosure: M.R. Mirza: Advisory board: Tesaro, Roche, AstraZeneca & Clovis Oncology. J. Wang, X. Wang, Z.Y. Zhang, V. Kanstra: Employment: Tesaro; Stock: Tesaro. M. Mau-Sørensen: Research grants and support to participate in conferences from Roche. S. Malander: Honoraria: AstraZeneca, Roche. All other authors have declared no conflicts of interest.
PROSPECTIVE COHORT STUDY OF BEVACIZUMAB PLUS STANDARD PLATINUM-BASED CHEMOTHERAPY AS FRONT-LINE TREATMENT FOR ADVANCED EPITHELIAL OVARIAN CANCER, FALLOPIAN TUBE CANCER, OR PRIMARY PERITONEAL CANCER: JAPANESE GYNECOLOGIC ONCOLOGY GROUP STUDY (JGOG3022)


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Background: The GOG-218 and ICON-7 studies showed that addition of bevacizumab (BEV) to front-line treatment for patients (pts) with advanced ovarian cancer increased progression-free survival. Based on this result, BEV has been widely used in the front-line treatment. However, sufficient safety information of addition of BEV is not available in Japan. This prospective cohort study is conducted to assess the safety of addition of BEV to front-line treatment.

Methods: Eligible pts have FIGO stage III–IV epithelial ovarian, fallopian tube or primary peritoneal carcinoma, were aged ≥20 years and have ECOG PS 0–2. Prior neoadjuvant chemotherapy was permitted. The primary cohort was defined as pts who received weekly paclitaxel/cisplatin (PC) plus BEV, and the exploratory cohort as pts who received other platinum-based regimen plus BEV. BEV is continued at the same dose as a single agent until disease progression or unacceptable toxicity. The primary objective is to assess safety (NCI-CTCAE v4.03) of the primary cohort.

Results: A total of 346 pts (Primary/exploratory cohort: 303/43) were enrolled from 79 institutions from Apr 2015 to Feb 2016. The data of primary cohort of 293 pts were analyzed on May 31, 2017. The median age was 58 years (range: 27–85). The majority of the histologic type was Serous adenocarcinoma (65.2%) followed by Clear cell adenocarcinoma (12.3%) and Endometroid adenocarcinoma (10.6%). Up-front surgery was performed in 203 pts (69.3%), and interval debulking surgery following neoadjuvant chemotherapy was performed in 90 pts (30.7%). A total of 45 serious adverse events occurred. Two pts (0.6%) developed a gastrointestinal perforation (grade 2) or fistula (grade 3). Thromboembolic events, hypertension, and hematoma of grade 3 or greater occurred in 3 (1.9%), 2 (0.7%), and 1 (0.3%), respectively.

Conclusions: Addition of bevacizumab to platinum-based front-line chemotherapy can be safely administrated for advanced ovarian cancer pts in Japan. The rates of gastrointestinal and thromboembolic toxicity were relatively low as compared with the previous studies.

Clinical trial identification: JGOG3022

Legal entity responsible for the study: Japanese Gynecologic OncoLgy Group Funding: Chugai Pharmaceutical Co., Ltd.

Disclosure: All authors have declared no conflicts of interest.

A LANDMARK ANALYSIS OF OVERALL SURVIVAL IN PR-OC PATIENTS TREATED WITH CHEMOTHERAPY AND BEVACIZUMAB USING EARLY TUMOR SHRINKAGE AS COVARIATE

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Background: We aimed at developing a OS model incorporating TK metrics in platinum-resistant (PR) ovarian cancer (OC) patients using data from the randomized, open-label phase 3 AURELIA trial designed to compare PFS in patients treated with chemotherapy alone (CT) or in combination with Bevacizumab (B). By means of a non-linear mixed effect TK model accounting for the dynamics of tumor growth, drug effect and treatment resistance was used to fit the TK to the AURELIA data.

Methods: Individual data from 361 patients randomly allocated to the B+CT or CT were available. Three types of CT were evenly distributed in both arms. Tumor size reported as sum of lesion diameter (SLD, RECIST 1.0) was collected at baseline and every 8 to 9 weeks until disease progression. Patients continued to be followed for OS even after treatment discontinuation. A non-linear mixed effect TK model accounting for logistic regression models suggested a higher risk of non-haematological AEs in pts with CV comorbidities (odds ratio (OR) adjusted for key prognostic factors: 1.75 p = 0.099) or HTN (OR 1.89; p < 0.001) and of CV events in pts with CV comorbidities (OR 3.12; p < 0.001). There was no relevant difference in progression-free survival (PFS) between subgroups. Further subgroup analyses of PFS according to HTN (pre-existing vs treatment emergent vs none) suggested the longer PFS in 132 pts of low HTN and HTN patients plus Hgb therapy (median PFS 26.5 mo). However, a Cox regression analysis to account for the confounding effect of BEV duration indicated that HTN development was not a significant predictive factor for OS.

Conclusions: In AURELIA, pts with comorbidities had similar PFS to the overall population, despite older age and worse ECOG PS. Grade 3/4 AEs were slightly more common, particularly in pts with diabetes mellitus, but did not lead to treatment discontinuation. These post hoc analyses suggest that with appropriate care, BEV is an option in pts with comorbidities.

Clinical trial identification: NCT01697488

Legal entity responsible for the study: Roche Pharma AG

Funding: Roche Pharma AG

Disclosure: H. Woopen: Membership on advisory board or board of directors: Roche Pharma AG. P. Wimmerberger: Membership on advisory board or board of directors: Roche Pharma AG. Mustea: Membership on advisory board or board of directors: Roche Pharma AG. F. Jaminion, F.J. Mercier: Employee of F. Hoffmann-La Roche Ltd. P. Wimberger: Membership on advisory board or board of directors: Roche Pharma AG.
Background: In metastatic breast cancer, bevacizumab (Bev)-based treatment beyond progression (TPB) has been found a valid option, whereas TPB with Bev in tubouvarian carcinoma (TOC) has not been intensively investigated so far. This retrospective study sought to investigate the feasibility and effectiveness of multiple lines of Bev-based systemic therapy (Tx) in patients (pts) with recurrent TOC.

Methods: From our database, a total of 90 pts with recurrent TOC (45 with platinum-based Tx until progression, overall survival was calculated from the start of the first Bev-based Tx) were identified. 37 (41.1%) pts had one, 20 (22.2%) two, 13 (14.4%) three, and 20 had 4-9 lines (p < 0.0001).

Results: Most frequent side effects of Bev were proteinuria occurring in 50%, hypertension in 41%, gastrointestinal toxicity in 33%, and infection in 17% of treatments. However, G3-4 toxicities were rare with hypertensive crisis in 2.2%, bowel obstruction in 0.9%, bowel perforation in 0.9%, nephrotic syndrome in 0.4% and infection seen in 1.3% of treatments. Both TTP and OS did not differ between different types of TPs. TTP: Bev, 5.4 months (mts); Bev+cis, 6.1 mts; Bev+mCx, 6.3 mts. OS: Bev, 28.6 mts, Bev+cis, 31 mts; Bev+mCx, 21.4 mts. TTP for platinum-resistant vs platinum-sensitive pts was 4.5 and 7.6 mts (p = 0.044). TTP was comparable between one and multiple lines of Bev: one line, 6.6 mts; two lines, 6.3 mts; three lines 5.9 mts; and 4-9 lines 3.7 mts (p = 0.130). However, OS increased significantly with the number of Bev-based lines of Tx. One line, 8.8 mts; two lines, 16.8 mts; three lines 25.4 mts; 4-9 lines, 36.6 mts (p < 0.0001).

Conclusions: Our results demonstrate that retreatment with Bev can be safely given to pts with recurrent TOC in the clinical routine. The incidence of severe side effects was generally low and did not increase by the line of Bev-based Tx. However, the number of Bev-based lines had a significant impact on overall survival. Thus, rechallenge with Bev may be a valuable option in the treatment of recurrent TOC.

Legal entity responsible for the study: Christian M. Kurbacher
Funding: None
Disclosures: C.M. Kurbacher: Author received honoraria from Roche, Amgen, Novartis, Teva Oncology, Riems. All other authors have declared no conflicts of interest.

957P Feasibility and effectiveness of multiple lines of bevacizumab-based therapy in patients with recurrent tuboovarian carcinoma

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957B Impact of body mass index (BMI) on outcome in 785 patients (pts) receiving systemic chemotherapy (CT) and bevacizumab (BEV) for primary advanced ovarian cancer (OC) (on behalf of the North-Eastern German Society of Gynaecological Oncology, NOGGO)

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1Department of Gynecology and Gynecologic Oncology, Charité Campus Virchow Klinikum, Berlin, Germany, 2Gynecology, University Medicine Greifswald, Greifswald, Germany, 3Gynecologic Oncology, Prawinklinik Krebskunde fuer Frauen, Berlin, Germany, 4C/o Charité Medical University of Berlin, North-Eastern German Society of Gynaecological Oncology (NOGGO e.V.), Berlin, Germany, 5Statistics, Data Management and Medical Informatics, IOMEDICO AG, Freiburg, Germany, 6Biostatistics and Epidemiology, Roche Pharma AG, Grenzach-Wyhlen, Germany, 7Medical Affairs, Roche Pharma AG, Grenzach-Wyhlen, Germany

Background: The GOG-0218 and ICON7 randomised phase III trials demonstrated the efficacy and safety of front-line BEV + CT for OC. The single-arm OTILIA study is evaluating BEV + CT in German clinical practice. In a previously reported interim analysis (ESMO & IGCS 2016), the observed safety and effectiveness were consistent with phase III results (preliminary median progression-free survival [PFS] 21.7 months). To address the lack of data on the impact of BMI on safety and clinical outcome in pts receiving CT + BEV, we performed exploratory analyses of the OTILIA dataset.

Methods: In OTILIA (NCT01697488), pts with FIGO stage IIIb–IV OC received front-line BEV + CT according to the EU label. Adverse events (CTCAE v4.0) were recorded at each cycle. Investigators assessed response per local practice. We performed post hoc exploratory subgroup analyses of the third interim dataset according to BMI and a multiple Cox regression analysis of PFS vs BMI age, ECOG performance status, FIGO stage, residual disease and ascites as covariates.

Results: BMI was available for 785 of 808 pts. Treatment duration was similar across BMI subgroups (Table). There were no significant differences in PFS between

Table: 956P

<table>
<thead>
<tr>
<th>Baseline characteristic, n (%)</th>
<th>All pts (n = 808)</th>
<th>Pts with CV comorbidities (n = 445)</th>
<th>Pts with pre-existing HTN (n = 406)</th>
<th>Pts with diabetes mellitus (n = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;70 y</td>
<td>382 (47)</td>
<td>262 (59)</td>
<td>252 (62)</td>
<td>52 (63)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>297 (37)</td>
<td>144 (32)</td>
<td>133 (33)</td>
<td>24 (29)</td>
</tr>
<tr>
<td>1</td>
<td>378 (47)</td>
<td>219 (49)</td>
<td>199 (49)</td>
<td>38 (46)</td>
</tr>
<tr>
<td>2</td>
<td>72 (9)</td>
<td>44 (10)</td>
<td>39 (10)</td>
<td>11 (13)</td>
</tr>
<tr>
<td>Ongoing CV comorbidities</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Pre-existing HTN</td>
<td>445 (55)</td>
<td>445 (100)</td>
<td>406 (100)</td>
<td>67 (81)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>83 (10)</td>
<td>67 (15)</td>
<td>64 (16)</td>
<td>83 (100)</td>
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<tr>
<td>No macroscopic residuum</td>
<td>220 (27)</td>
<td>120 (27)</td>
<td>107 (26)</td>
<td>18 (22)</td>
</tr>
<tr>
<td>Ascites &gt;500 mL</td>
<td>99 (12)</td>
<td>63 (14)</td>
<td>57 (14)</td>
<td>9 (11)</td>
</tr>
<tr>
<td>Grade 3/4 AEs</td>
<td>301 (37)</td>
<td>189 (42)</td>
<td>177 (44)</td>
<td>42 (51)</td>
</tr>
<tr>
<td>Treatment discontinued</td>
<td>433 (54)</td>
<td>233 (52)</td>
<td>209 (51)</td>
<td>50 (60)</td>
</tr>
<tr>
<td>Reason for treatment discontinuation</td>
<td>134 (17)</td>
<td>72 (16)</td>
<td>69 (17)</td>
<td>12 (14)</td>
</tr>
<tr>
<td>Disease progression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 mo documentation completed</td>
<td>82 (10)</td>
<td>43 (10)</td>
<td>33 (8)</td>
<td>7 (8)</td>
</tr>
<tr>
<td>Treatment-related AEb</td>
<td>67 (8)</td>
<td>38 (9)</td>
<td>37 (9)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Patient request</td>
<td>47 (6)</td>
<td>20 (4)</td>
<td>17 (4)</td>
<td>8 (10)</td>
</tr>
<tr>
<td>Death</td>
<td>19 (2)</td>
<td>15 (3)</td>
<td>12 (3)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Median BEV duration, mo (range)</td>
<td>13.4 (12.8–13.8)</td>
<td>13.4 (12.5–13.8)</td>
<td>13.5 (12.5–13.8)</td>
<td>11.3 (8.1–13.6)</td>
</tr>
<tr>
<td>Median PFS, mo (95% CI)</td>
<td>21.3 (20.3–22.5)</td>
<td>21.3 (20.1–23.1)</td>
<td>21.3 (20.2–23.1)</td>
<td>20.2 (16.8–26.2)</td>
</tr>
</tbody>
</table>

*ECOG PS 3 in 14 pts, missing/unknown in 47 pts.
*Reported as ‘side effects of therapy’ until Aug 2013. ECOG PS a 0 297 (37) 144 (32) 133 (33) 24 (29)

Age/C21 Median age, y (range) 68 (26–83) 71 (33–83) 72 (33–83) 72 (46–83)

Grade 3/4 AEs 301 (37) 189 (42) 177 (44) 42 (51)

Death 19 (2) 15 (3) 12 (3) 3 (4)
subgroups with BMI ≤20 (hazard ratio [HR] 1.27; 95% CI 0.92–1.77) or ≥30 (HR 1.33; 95% CI 0.98–1.81) vs 20–25 kg/m² (Cox regression model) but in pts with a BMI ≤20 kg/m², numerically more grade 3/4 and serious adverse events were observed.

Conclusions: In these post hoc exploratory analyses we were unable to identify any clear effect of BMI on PFS. The tolerability of BEV + systemic CT for advanced OC appeared to be influenced by BMI.

Clinical trial identification: NCT01697488

Legal entity responsible for the study: Roche Pharma AG

Funding: Roche Pharma AG

Disclosure: J. Sehouli: Membership on advisory board or board of directors: Roche. S. Klawitter, A. Wegenar: Employment: Roche Pharma AG. P. Wimberger: Membership on advisory board or board of directors: Roche, Novartis, Amgen, AstraZeneca, MSD, TEVA, PharmaMar, Fresenius Biotech; Corporate-sponsored research: Roche, Novartis, Amgen, Fresenius Biotech, MSD. All other authors have declared no conflicts of interest.

A prospective study to evaluate the role of Cytoreductive surgery (CRS) + HIPEC in advanced epithelial ovarian malignancy -100 consecutive cases -INDIAN experience

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Background: To study the outcome and role of cytoreductive surgery (CRS) + HIPEC in advanced upfront and recurrent epithelial ovarian cancer.

Methods: 100 consecutive patients with advanced epithelial ovarian cancer diagnosed between January 2011 to January 2017 were included in study after informed consent. IRB ethical clearance was obtained. All patients underwent CRS followed by HIPEC with dedicated machine (PERFORMER-RET) using only cisplatin 45mg/m² for upfront and cisplatin 45mg/m² and adriamycin 15mg/m² in recurrent cases for 90 minutes in semiclosed technique at 42 degrees Celsius. Descriptive study statistical analysis was done.

Results: Out of 100 patients, 74 were primary and 26 recurrent. Of 74 cases, 67.5% (n = 50) had upfront CRS + HIPEC and 32.5% (n = 24) had interval CRS + HIPEC. Of 26 recurrent, 69.3% (n = 18) were platinum sensitive and 30.7% (n = 8) were platinum resistant. Median age 54.5(22-78) PCI 11.9(3-57) duration of surgery 9.5 hrs (5-15),GI recovery 5.4 days, hospital stay 11.4 days. 12% (grade III) adverse morbidity and 3% 60 day mortality. Prolonged duration of surgery (p = 0.001), multivisceral resection (p = 0.039) hypoalbuminemia (p = 0.04) hypocalcemia (p = 0.01) were predictive factors for morbidity and prolonged hospital stay. Primary ovarian malignancies and platinum sensitive benefit the most with CRS + HIPEC whereas platinum resistant disease does not have any benefit. Legal entity responsible for the study: IRB ethical clearance, institutional ethical board clearance Funding: None Disclosure: All authors have declared no conflicts of interest.

Table: 958P

<table>
<thead>
<tr>
<th>Parameter, n (%)</th>
<th>BMI, kg/m²</th>
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<tbody>
<tr>
<td></td>
<td>&lt;20 (n = 107)</td>
</tr>
<tr>
<td>Age ≥70 years</td>
<td>35 (33)</td>
</tr>
<tr>
<td>ECOG performance status ≥2</td>
<td>13 (12)</td>
</tr>
<tr>
<td>Median BEV duration, months (95% CI)</td>
<td>12.5 (10.3–13.6)</td>
</tr>
<tr>
<td>BEV discontinued</td>
<td>67 (63)</td>
</tr>
<tr>
<td>Main reason for discontinuing BEV</td>
<td>Disease progression</td>
</tr>
<tr>
<td></td>
<td>23 (21)</td>
</tr>
<tr>
<td>Grade 3/4 adverse events</td>
<td>All</td>
</tr>
<tr>
<td></td>
<td>113 (34)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>19.4 (16.0–21.7)</td>
</tr>
</tbody>
</table>

*Reported as ‘side effects of therapy’ until Aug 2013.

960P

Role of laparotomy-based parameters in assessment of optimal primary debulking surgery and long-term outcomes in patients with stage IIIIC epithelial ovarian cancer

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Background: We evaluated the ability of our newly developed laparotomy-based model to predict optimal primary debulking surgery (PDS) and long-term outcomes of stage IIIIC epithelial ovarian cancer (EOC).

Methods: Data of 400 IIIC EOC patients who underwent laparotomy were retrospectively analyzed to investigate predictors of optimal PDS. Parameters including infiltration of the bowel, peritoneum, diaphragm, hepatic surface, spleen, and stomach; omental caking; mesenteric retraction; and metastasis of the pelvic and para-aortic lymph nodes increased the difficulty of surgery. The parameters with a specificity ≥75%, positive predictive value ≥50%, and negative predictive value ≥30% were included in the final predictive index value (PIV) model. Each parameter was assigned a score based on the strength of its statistical association, and a total PIV was tabulated for each patient. Receiver operating characteristic (ROC) curve analysis was performed to assess the predictive ability of the model. Subgroup analyses were performed in patients with RD > 1 cm and ≤1 cm.

Results: After PDS, 223 (55.8%) patients with RD ≤1 cm had longer progression-free survival (PFS) and overall survival (OS) than patients with RD > 1 cm (PFS: 24.3 vs. 15.9 months; P < 0.001 and OS: 48.6 vs. 35.6 months; P < 0.001). Nine parameters (excluding pelvic lymph node metastasis) were assigned a PIV of 2. Patients with a PIV of ≥14 were more likely to undergo suboptimal PDS with a specificity of 100%. The area under the ROC curve of our PIV model was 0.753. Among patients with RD ≤1 cm, those with a PIV < 2 had longer PFS and OS. Among patients with RD ≥1 cm, those who were sensitive to platinum had longer PFS and OS, there was no difference in PFS and OS between patients with and without combined multiple-organ resection, and the median PFS of patients with a lymph node rate of ≥32.5% was shorter than in patients who did not undergo lymph node dissection, but the difference in OS was not significant.

Conclusions: When PDS left RD ≤1 cm, patients with a PIV of < 2 had a better prognosis. When PDS left RD > 1 cm, patients who were sensitive to platinum had a better prognosis. Additionally, patients with a lymph node rate of ≥32.5% were more likely to progress. Legal entity responsible for the study: no Funding: None Disclosure: All authors have declared no conflicts of interest.
were classed low-use (at 1Health Economics and Outcomes Research, TESARO, Inc., Waltham, MA, USA, ICON7 randomised 1528 pts 1:1 to reference treatment

Results: lysis techniques and methods appropriate for data with non-proportional hazards were

(mths) and retreated with platinum. The association between 1st line bev and OS was

high or low platinum use, from the proportion of their pts progressing in 0-8 months

(excl. maintenance bev) and also varied between centres. We categorised centres as

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E. Pujade-Lauraine 5, A.M. Oza 6, T. Perren 7

The ICON7 trial reported increased progression-free survival with beva-

cizumab (bev) added to platinum-based chemotherapy in newly diagnosed ovarian cancer, and increased overall survival (OS) in a poor prognosis subset. Most patients (pts) had further chemotherapy following progression. On average, pts receiving bev had later progression and were thus more likely to receive further platinum. We investigat-

gated the effect of second-line treatment type on the association between first-line bev and OS.

Methods: Second line chemotherapy regimens were categorised as platinum-containing or other. Platinum reuse varied with time to progression after end of 1st line (exclusive maintenance bev) and also varied between centres. We categorised centres as high or low platinum use, from the proportion of their pts progressing in 0.8 months (mths) and retreated with platinum. The association between 1st line bev and OS was analysed separately at low-use centres and at high-use centres. Standard survival analysis techniques and methods appropriate for data with non-proportional hazards were used.

Results: ICON7 randomised 1528 pts 1:1 to reference treatment +/ bev. Reference pts were more likely to experience disease progression (98 mths (38% v 24%)). Reuse of platinum varied with time to progression; 37% at 0-5 mths; 76% at 6-8 mths; 94% at 9 mths. 174 centres (covering 1290 pts) had ≥1 progression at 0-8 mths; 76 centres were classed low-use (<50% platinum 2nd line in 0-8 mths) and 98 high-use. The earlier progression of reference pts resulted in fewer getting 2nd line platinum at low use centres (41% v 56%), but not at high-use centres (76% v 77%). There was evidence of significantly shorter OS among reference pts at low-use centres (p = 0.05, restricted mean survival 44.1 v 49.0 mths), but not at high-use centres (p = 0.20, restricted mean survival 52.2 v 50.0 mths).

Conclusions: Improved OS with bevacizumab may result from an association with platinum-containing second-line treatment: bev increases time to progression, increased time to progression increases the likelihood of second-line platinum, second line platinum increases OS. It is possible therefore that OS might be improved using a lower time threshold for second-line platinum chemotherapy, whether or not bevacizumab has been used.

Clinical trial identification: ISRCTN: 91273575

Legal entity responsible for the study: ICON7 was a GCIG trial, overall sponsor is Medical Research Council, UK.

Funding: Medical Research Council Clinical Trials Unit at University College London

Disclosure: All authors have declared no conflicts of interest.

Disease burden during the “watchful waiting” period in patients with recurrent ovarian cancer

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Background: The standard of care for patients (pts) with recurrent ovarian cancer (OC) who respond to platinum-based chemotherapy has been “watchful waiting”. While studies have shown that pts experience anxiety and fear of recurrence during watchful waiting, the rate of serious clinical events that require hospitalizations or emergency room (ER) visits during this observation period has not been examined. The objective of this study was to assess the rate of such events using a claims database.

Methods: This retrospective study identified pts newly diagnosed with OC in January 2009 to September 2015 in MarketScan® Commercial and Medicare Supplemental Databases (US). Pts with commercial or Medicare coverage for 12 months prior to and ≥1 month after first diagnosis were included. Recurrence was defined by the presence of 2nd line platinum-based therapy, and watchful waiting as the period without active treatment following chemotherapy. Rate of inpatient admissions and ER visits during watchful waiting were assed.

Results: 312 pts were identified who had a treatment-free interval after 2nd line platinum treatment. During this watchful waiting period (median duration, 162 days), 30.1% had an inpatient admission and 27.4% had an ER visit. Median time to first hospitalization from end of 2nd-line chemotherapy was 56 days, and median time to first ER visit was 68 days. There was a total of 650 inpatient hospitalizations, for an average of 0.5 per pt. Mean length of stay per hospitalization was 10 days. Top 5 reasons for hos-

pitalsizations were (1) intestinal obstruction without mention of hernia (13.5%), (2) secondary malignant neoplasm of respiratory and digestive systems (10.3%), (3) malignant neoplasm of ovary and other uterine adnexa (9.2%), (4) septicemia (4.5%), and (5) secondary malignant neoplasm of other specified sites (4.2%).

Conclusions: A substantial proportion of 2nd-line recurrent OC pts were hospitalized or had ER visits during the watchful waiting period post platinum treatment. The tim-

ing of these hospitalizations suggests that they were not necessarily related to progres-
sion but rather reflective of the ongoing disease burden patients experience during this “watching” period.

Clinical trial identification: NCT01847274

Legal entity responsible for the study: TESARO, Inc.

Funding: TESARO, Inc.

Disclosure: B. Harroz, K. Travers, M. Bala: Employment: Tesaro; Stock: Tesaro. B. Davis, A. Gigliana: Employment: Truven Health Analytics. All other authors have declared no conflicts of interest.
Results

Table: 965P PFS subgroup analysis for pts with CR or PR at study entry

<table>
<thead>
<tr>
<th></th>
<th>Olaparib</th>
<th>Placebo</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>91</td>
<td>47</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>NR</td>
<td>5.6</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.26 (0.16–0.42)</td>
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<tr>
<td>Pts with PR at study entry</td>
<td>105</td>
<td>52</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>13.8</td>
<td>5.5</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.37 (0.25–0.54)</td>
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</table>

*One patient in the olaparib arm did not receive study treatment. HR, hazard ratio; NR, not reached

At study entry, 73/196 (37%) olaparib pts and 35/99 (35%) placebo pts had measurable disease (evidence of target lesions at baseline); within this group, the adjusted objective response rate (number of pts with CR and PR divided by the number of pts with measurable disease at baseline) was 41.1% with olaparib vs 17.1% with placebo (odds ratios 3.52, 95% CI 1.34–10.39; P = 0.0097). The placebo value is higher than expected, possibly due to a carry-over effect from last chemotherapy. In the olaparib arm, 17/113 pts (15.0%) with evidence of disease at baseline achieved CR following maintenance therapy (placebo arm, 5/35 [14.3%]).

Conclusions: Treatment with olaparib not only maintained the response achieved with PBC, but also induced additional antitumour activity in pts with measurable target tumour lesions at baseline. Olaparib monotherapy led to a significant PFS benefit in pts with both CR or PR at study entry, further supporting the role of olaparib as maintenance treatment for pts with PSROC and a platinum-sensitive relapsed ovarian cancer (OC) in a GINECO cohort study.
free interval (PFI) of 6-12 months. The aim of this work was to assess the clinical impact of the combination when used in routine practice.

Methods: This was a prospective, multicenter study carried out in 25 French centers. Eligible patients (pts) were women ≥18 years old with histologically proven relapsed disease following at least one platinum-based chemotherapy and candidates to receive T (1.1 mg/m²) plus PLD (30 mg/m²). Analysis was performed according to the PFI subgroups (PFI 6-12 and PFI 12 (fully platinum-sensitive)) as stated in a B software.

Results: From 2007 to 2016, 91 pts with platinum-sensitive OC were included (median age 65 years old, range: 42–86). Most pts had PFI 6-12 (n = 58, 63.7%) vs. n = 33 with PFI 12. Pts were treated with a median of 6 cycles (range: 1–12) of T-PLD. 47 (51.6%) pts received T-PLD as ≥3° line of chemotherapy (range: 2–8). The toxicity profile in the PFI subgroups was different from that of the overall population. The number of pts with grade 3/4 hematological toxicities in the PFI 6-12 and PFI >12 co- horts was: neutropenia 29.6%/17.6%, febrile neutropenia 4.4%/3.3%, thrombocytopenia 7.9%/6.8%, anemia 5.5%/2.2%. Grade 3/4 band and foot syndrome (1 pt) and mucositis (1 pt) were observed in the PFI 12 group. Increases in transaminases (grade 3/4) were experienced by 11 pts (10/1) in the PFI 6-12 group and by 5 pts (4/1) in the PFI >12 group. 3 pts in the PFI 6-12 group and 3 in the PFI >12 group discontin- uated treatment because of toxicities, 6 and 3 due to premature death. Partial and com- plete responses were achieved in 43 pts (PFI 6-12: n = 26; PFI ≥12: n = 17; p = 0.82). Median PFS after T-PLD was 5.9 months (95% CI 4.9–6.7) in the PFI 6-12 group and 5.8 months (95% CI 5.7–8.5) in the PFI >12 group. OS data were not mature at the time of this analysis.

Conclusions: The safety profile of T-PLD when used in real-life management of non- selected OC is similar to that observed in clinical trials. T-PLD remains a valuable alternative treatment of toxicities, 6 and 3 due to premature death. Partial and complete responses were achieved in 43 pts (PFI 6-12: n = 26; PFI ≥12: n = 17; p = 0.82). Median PFS after T-PLD was 5.9 months (95% CI 4.9–6.7) in the PFI 6-12 group and 5.8 months (95% CI 5.7–8.5) in the PFI >12 group. OS data were not mature at the time of this analysis.

967P | An observational, multicenter, prospective study of trabectedin plus pegylated liposomal doxorubicin (PLD) in platinum-senstive recurrent ovarian cancer (PSROC)
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Background: The OVA-YOND prospective non-interventional phase IV study evaluated trabectedin plus PLD in real-life clinical practice to assess the toxicity and efficacy of the combination when given in accordance with the marketing authorization to women with PSROC.

Methods: Data from patients treated with PLD 30 mg/m² and immediately followed by trabectedin 1 mg/m² by i.v. infusion every 3 weeks have been collected.

Results: From 2012 to 2016, 77 enrolled patients from 31 sites across Germany who received at least one cycle of trabectedin plus PLD were evaluated. All patients had a platinum-sensitive relapse with a median platinum-free interval of 12 months (range: 6- 86 months). Median age of patients was 66 years (range: 60-78) and 80.5% had ECOG performance status 0/1. Serous carcinoma was the most prevalent histological type (n = 54, 70.3%), followed by clear cell carcinoma (12.2%). Grade 3/4 neutropenia (18.2%) and thrombocytopenia (15.6%), thrombocytopenia (9.1%), ALT (7.8%) and AST (6.5%) increase, and nausea/ vomiting (5.2%) each. No grade 5 or unexpected TRAE occurred. dFdCTP levels were increased 25% by the addition of carboplatin. The RP2D was 500 mg/m² NUC-1031 on days 1 & 8 with carboplatin. The safety, RECIST response, PFS and PK/PD.

Conclusions: NUC-1031 combined with carboplatin is well tolerated and effective in recurrent platinum resistant and sensitive OC. dFdCTP levels were increased 25% by the addition of carboplatin. The RP2D was 500 mg/m² NUC-1031 on days 1 & 8 with AUC5 carboplatin day 1, q21d. The efficacy and synergy of this schedule and the ability to deliver carboplatin at AUC5 makes this an attractive therapeutic combination.

968P | Phase 1/2 trials of peptides cocktail vaccine for resistant cervical and ovarian cancer: Qol analysis
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Background: We conducted phase 2 (P2) studies of peptides vaccine (PV) immuno- therapy for cervical (CC) and ovarian cancer (OC) using HLA-restricted tumor specific peptides and VEGF receptor 1 (R1) and 2 (R2) adenocarcinoma. As for OV, 402, PV of CC and OV was 4.9 m (0.6-76.6 m).

Methods: Heavily treated CC and OC with A02 or A24 within ECOG PS 2 were candi- dates. Fully written-IC had obtained. PV cocktails were as follows: for OC of A24 comprised FOXM1, MELK, HJURP, VEGFR1 (R1) and R2. As for OV, 402, PV of CC and OV comprised of URLC10 and HIG2. Each peptide was mixed at a dose of 1 mg/kg. 39 patients were included in the study. The P1 showed feasible (presented in ECCO2013), and further P2 had completed in 66 accruals and the results showed efficacy (ASCO2015 S567). Approval of IRB had obtained. This time, QOL study using QLC-C30 had analyzed and survival data were up-dated.

Conclusions: Trabectedin plus PLD confer clinically meaningful benefit to patients with PSROC, being either comparable or better to those previously observed in selected popula- tion from clinical trials or other real-life studies, and with a manageable safety profile.

Clinical trial identification: NCT01864900, OVA-YOND

Legal entity responsible for the study: PharmaMar

Disclosure: P. Wimberger: Honoraria for scientific talks from Pharma Mar. All other authors have declared no conflicts of interest.
Background: Selinexor (S) is an oral, first in class, inhibitor of exportin 1 (XPO1). In a Phase II clinical trial of pts with relapsed ovarian cancer (OC) and endometrial cancer (EC), single agent S, demonstrated anti-cancer activity. In addition, clinical exploratory analysis has demonstrated S target engagement and a relationship between baseline circulating tumor cells and duration of response. Here we report results of a Phase I study evaluating safety/tolerability of S combined with C and P in pts with advanced OC and EC or carcinomaoma.

Methods: Patients (Pts) were enrolled using 5 + 3 dose escalation design for each regimen (reg). All pts with OC received 1 prior platinum (pt) therapy. Pts with EC could be chemotherapy naive or have received 1 prior pt therapy. Pts were enrolled to 1 of 4 regimens regardless of disease type as described in Table. Response was evaluated Q9 weeks (RECISt 1.1).

Results: 16 pts (12 OC, 3 OC, 1 endometrial carcinoma) were enrolled. 1 drug related DLT of G3 syncope occurred on Reg 2. Most common G2 AEs were hyperglycemia (43.8%), leukopenia (43.8%), anemia (31.3%). Most common Grade 3 and 4 AEs were anemia (62.5%), neutropenia (37.5%), lymphopenia (43.8%), neutropenia (31.3%) thrombocytopenia (12.5%). 50% of evaluable pts on Reg 1 and 2 were dose reduced due to toxicity. One dose reduction of S on Reg 3. There were no dose reductions on Reg 4. 13 pts were evaluable for efficacy: 2 CRs, 10 PRs, and 1 SD. Time on study ranged from 2–10.8 mos with 3 pts still on study.

Conclusions: Selinexor in combination with carboplatin and paclitaxel (CP) chemotherapy in advanced OC, EC, and carcinomaoma was well tolerated. The RP2Ds have been established at 30 mg/m² twice weekly of S and 60 mg flat dose weekly in combination with CP chemotherapy.

Table: 970P

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>Regimen details</th>
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<tr>
<td>1</td>
<td>4</td>
<td>C AUC5 (day 1), P 175 mg/m² (day 1) and S 30 mg/m² (days 1, 4, 8, 11, 15, 18)</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>C AUC5 (day 1), P 80 mg/m² (days 1, 8, 15) and S 30 mg/m² (days 1, 4, 8, 11, 15)</td>
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<tr>
<td>3</td>
<td>3</td>
<td>C AUC5 (day 1), P 80 mg/m² (days 1, 8, 15) and S 60 mg (days 1, 8, 15)</td>
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<tr>
<td>4</td>
<td>3</td>
<td>C AUC5 (day 1), P 175 mg/m² (day 1) and S 60 mg (days 1, 8, 15)</td>
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Clinical trial identification: NCT02269293

Legal entity responsible for the study: Kenalog Kettering Cancer Center

Funding: Kyoropharm Pharmaceuticals

Disclosure: All authors have declared no conflicts of interest.

Annals of Oncology

971P

Pazopanib and oral cyclophosphamide in women with platinum resistant epithelial ovarian cancers

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Background: Women with recurrent, multiply treated epithelial ovarian cancer (EOC) have unfavorable prognosis with limited treatment options after failure of platinum based regimens. Antiangiogenic therapies have shown some efficacy in these patients. We report here a retrospective analysis of women with recurrent, platinum resistant EOC treated with an oral regimen of anti-angiogenic agent Pazopanib and Cyclophosphamide.

Methods: Women with histologically proven recurrent platinum-resistant EOC were treated with tablets pazopanib (600 mg p. o. daily in two divided doses, 400 mg and 200 mg) and cyclophosphamide (50 mg p. o. daily for 14 days every 21 days) until disease progression or unacceptable toxicity. Response was evaluated radiologically every 12 weeks.

Results: Eighteen patients (16 platinum resistant and 2 platinum refractory) were treated between April 2014 and April 2017 with a mean age of 50 (38–66) years and median (6–2) previous lines of chemotherapy. Including three patients with progressive disease on bevacizumab. Patients received a median of 2 (2–8) cycles of pazopanib and cyclophosphamide with partial response in 8 (44%) patients (including 1 of 3 prior bevacizumab treated patients), stable disease in 5 (28%) and disease progression in 5 (28%) patients, as best response. The median progression-free survival was 5.0 months. Common adverse events were fatigue (50%), diarrhea (50%), elevated liver enzymes (43%), mucositis (61%), myelosuppression (28%), skin toxicity (33%), hypertension (6%) and hair depigmentation (6%). Dose reduction due to toxicity was required in 11 (61%) patients and no patient stopped treatment due to toxicity.

Conclusions: Pazopanib and oral cyclophosphamide is a well-tolerated regimen with clinically relevant benefit in platinum resistant, epithelial ovarian cancer patients.

Clinical trial identification: This is a retrospective analysis of Platinum resistant epithelial ovarian cancer patients treated at our institute. The approval for doing this analysis was taken from Institute’s ethics committee.

Legal entity responsible for the study: Institutional Review Board Institutional Review Board, Tata Memorial Hospital, Mumbai, India

Funding: None

Disclosure: All authors have declared no conflicts of interest.

972P

Apatinib as a salvage treatment in gynecologic cancer patients failed from two or more lines of prior chemotherapy

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Background: Apatinib is an oral inhibitor of the vascular endothelial growth factor receptor (VEGFR)-2. There is currently no standard treatment for patients with gynecologic cancer who failed from ≥2 lines of chemotherapy. The purpose of this study was to evaluate the benefits and adverse events of apatinib in the treatment of patients with advanced cervical and ovarian cancer who failed from ≥2 lines of chemotherapy.

Methods: Patients with advanced cervical and ovarian cancer received at least two lines of prior chemotherapy before being treated with apatinib were retrospectively reviewed between April 2015 and January 2017. All included patients received continuous apatinib treatment until disease progression, death, or intolerable toxicity. Progression and toxicities were evaluated by the Kaplan-Meier method and according to NCI-CTC 3.0, respectively.

Results: Twenty-six patients were eligible (cervical cancer, n = 12 (46.2%); ovarian cancer, n = 14 (53.8%)). After apatinib dose adjustment, 14 patients (53.8%) received 500 mg/day, 8 received 250 mg/day, 3 received 425 mg/day, and one received 675 mg/day. The median progression-free survival (PFS) of cervical and ovarian cancer was 8 months (95% confidence interval (CI): 3.83–12.17) and 4 months (95% CI: 1.57–6.44), respectively. The objective response rates in cervical cancer and ovarian cancer were 50% (n = 6/12) and 50% (n = 7/14), respectively. The disease control rate was 100% (n = 12/12) for cervical cancer and 71.4% (n = 10/14) for ovarian cancer. No complete response was observed. The toxicities associated with apatinib were generally acceptable: eight patients (30.8%) developed grade 3/4 toxicity. The most common adverse events were hypertension (n = 17; 65.4%), hand-foot syndrome (n = 24, 92.3%), and mouth mucositis (n = 28, 76.9%).

Conclusions: Apatinib monotherapy could be a promising and tolerable treatment for patients with advanced/recurrent cervical and ovarian cancer who failed from two or more lines of chemotherapy.

Legal entity responsible for the study: Congying Xie

Funding: None

Disclosure: All authors have declared no conflicts of interest.
A GINECO phase II study of Navitoclax (ABT 263) in women with platinum resistant/refractory recurrent ovarian cancer (ROC)

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Background: Among ovarian cancer patients with early relapse after platinum chemo-therapy, there is no convincing active treatment. In preclinical studies, we previously demonstrated promising activity of Navitoclax (ABT-263), an anti-apoptotic inhibitor of Bcl-2 family, in ROC tumors, suggesting a potential action in platinum resistant pa-\n\ntients. In this prospective multicentric phase II study, we evaluated the efficacy of Navitoclax monotherapy in heavily pretreated ROC patients.

Methods: This study included high grade serous patients with platinum resistance. Navitoclax was orally administered at 150 mg/day during a lead in period (7 to 14 days) and then increased to 250 mg in the absence of dose-limiting thrombocytopenia (<50). Treatment was continued until disease progression or toxicity. PFS was the pri-\n\nmary endpoint. Response was also assessed using RECIST criteria. Analyses of Bcl-2 family proteins were also assessed.

Results: From January to September 2016, 47 patients were included in 13 institutions and 46 patients were analyzed: 44 ovarian carcinomas, 1 peritoneal carcinoma and 1 fallopian tube, median age 63 (38-80); BRCA1/2 mutations (n = 7), negative (n = 25) and un-\n\nknown (n = 14). The median number of prior treatment lines was 4 (2-12). PFS was 50 days [6-234] with 1 partial response (PR), 15 stable diseases (SD). Thrombocytopenia was the major side-effect, with G3 (n = 11) and G4 (n = 1) leading to maintain the dose at 150 mg for 8 patients and to treatment discontinuation for 3 patients. Neither sig-\n\nnificant bleeding nor toxic death was observed. 26 patients were treated after progression, 33 with chemotherapy (10 receiving platinum agent); among the 21 evaluable patients, 1 PR and 8 SD were observed, including 6 patients treated with platinum, with 3 long re-\n\nsponders (7 to 9 months). No BRCA1 mutation was observed among the responders.

Conclusions: Navitoclax monotherapy had modest activity without unacceptable tox-\n\nitity. However, as shown by response to treatment after progression, Navitoclax may re-\n\nverse platinum resistance in ROC patients. Complementary biological data in pro-\n\ngress may help select patients who could benefit from Navitoclax.

Clinical trial identification: EuDraCT number: 2015-00019-35 Clinical Trial Number: NCT023991095

Legal entity responsible for the study: Centre François Baclesse - CAEN

Funding: The French Cancer Research Hospital Program in 2011 & the Mariapia Bressan award in GINEGEPs 2014 Drug supply has been provided by Abbvie Laboratory

Disclosure: All authors have declared no conflicts of interest.

Reproductive function in patients (pts) with malignant ovarian germ cell tumors (MOGCT) following chemotherapy (CT)

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Background: MOGCT generally affect young women, grow rapidly, usually involve one ovary and are highly chemosensitive. Only a few studies have evaluated the reproductive outcomes of pts following CHT. The aim of this study was analysis of long-term effects of CHT on reproductive function in a large population of young women treated for MOGCT in our center.

Methods: Inclusion criteria in our study were MOGCT, fertility-sparing surgery, cis-\n\nplatin- and etoposide-based induction CHT (BEP/EP regimen), age under 40, no re-\n\n lapse following CHT at least 1 year. Blood tests were taken for hormones of ovarian function (follicle-stimulating hormone, luteinizing hormone, estradiol, anti-Mullerian hormone (AMH), inhibin B) to assess their menstrual, reproductive function, post-\n
terapeutic status of pregnancy or delivery.

Results: A total of 47/163 (28.8%) pts with MOGCT treated in our center between 1987-2015 satisfied to the criteria. Mean age was 21 years (range, 14-35). Median num-\n\nber of CHT cycles was 4 (range, 1-6). The 5-year OS was 85% for all pts and 100% for these 47 women. All pts recovered their menstrual function during the first year after completion of CHT. With median E-up 90 mo. (range, 12-228), 23/47 (49%) pts at-\n\ntempted conception, 18/23 (78.3%) women conceived with 20 live birth deliveries. There were 2/18 (11%) miscarriages and 6/18 (33.3%) terminations. Four women were pregnant at the moment of the analysis. Inhibin B level was normal in all 15 evaluated pts (median 74.4 pg/ml, range 10-120). Median of AMH level was 0.97 ng/ml (range 0.08-6). In 18 (52.6%) of 19 pts AMH level was <1 ng/ml, that considered a decrease of ovarian reserve. The quantity of pregnancies and deliveries, levels of hormones didn’t depend on the number of cycles.

Conclusions: Unilateral adnexectomy followed by modern cisplatin-based chemother-\napy does not adversely affect young women’s fertility and provides high chance for cure.

Legal entity responsible for the study: Russian Cancer Research Center

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Preoperative MRI versus intra-operative frozen section in surgical management of clinically early endometrial cancer

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Background: The role of systematic lymphadenectomy in clinically early stage endo-\nmetrial cancer is controversial. A number of factors can predict lymph node metastasis including myometrial invasion, tumor grade in endometrial cancers. The purpose of the present study is to evaluate the accuracy of preoperative MRI and intraoperative frozen section in determining the depth of myometrial invasion, cervical involvement, tumor size and lymph nodal status. We also studied the accuracy of clinical and intraoperative MRI for myometrial biopsy and intraoperative frozen section in determining the grade of the tumor.

Methods: Medical records of 160 consecutive cases of clinically early stage endometrial cancer were reviewed retrospectively. A record of depth of myometrial invasion, tumor size, cervical involvement and presence of enlarged lymph nodes was made on a pre-\n\noperative MRI. Similar depth of myometrial invasion, tumor size, cervical involvement and grade of the tumor were recorded on an intraoperative frozen section. The grade of the tumor was also recorded on a preoperative endometrial biopsy. Standard statistical calculations were used.

Results: The sensitivity and specificity of MRI for myometrial invasion was 83.1% and 75.5%, respectively while that for frozen section were 80 and 96.2%, respectively. For tumor grade the sensitivity and specificity of preoperative endometrial biopsy were 80 and 95.6%, respectively while that of frozen section were 53.8 and 97.6%, respectively. For cervical involvement the sensitivity of MRI and frozen section was 62.5 and 98.4%, respectively.

Conclusions: Although the sensitivity of both frozen section and MRI for predicting deep myometrial invasion was similar (80 vs 81.3%) but the specificity (96.2 vs 75.5%) and negative predictive value (92.7 vs 88.2%) of frozen section were superior to MRI. Both preoperative biopsy and intraoperative frozen section had low sensitivity (60 vs 55.8%) for detecting a high-grade lesion.

Legal entity responsible for the study: Institutional ethics committee, Tata Memorial Centre

Funding: None

Disclosure: Author has declared no conflicts of interest.

Impact of the adjuvant management and risk factors on survival in FIGO stage 3 endometrial cancer patients

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Background: Patients with FIGO stage 3 endometrial cancer often receive adjuvant therapy, but level I evidence is lacking. The purpose of this study was to evaluate the
relapse-free survival (RFS), disease-free survival (DFS) and overall survival (OS) in patients with FIGO stage 3A to 3C patients by treatment modality received and risk factors.

Methods: Consecutive patients with FIGO stage 3 endometrial cancer treated from 2000-2010 were identified in the provincial cancer registry. Clinicopathologic characteristics, adjuvant treatments and outcomes were compared using descriptive and multivariable analyses.

Results: 261 patients had stage 3 endometrial cancer, 132 with stage 3A, 9 with 3B, 85 with 3C1 and 35 with 3C2. 39 had FIGO grade 1 disease, 75 grade 2, 147 grade 3. 5 had endometrioid and 35 had serous carcinoma. 170 (65%) had >50% myometrial invasion; 162 (62%) had presence of LVI. 161 patients received both adjuvant chemotherapy (CT) and radiotherapy (RT); 33 received RT only; 32 received CT only; 35 received neither. 5-year (5Y) RFS, DFS and OS were similar among stage IIIA (RFS 55.1%, DFS 46.7%, OS 58.5%), IIIB (RFS 50.8%, DFS 50.8%, OS 58.5%), IIIC1 (RFS 45.4%, DFS 44.1%, OS 49.9%) and IIIC2 (RFS 42%, DFS 42%, OS 41.6%). Use of adjuvant RT was associated with improved median RFS (57.2 vs. 16.9m, p < 0.0001), DFS (53.7 vs 14.7m, p < 0.0001) and OS (61.9 vs 25.7m, p < 0.0001) compared to no RT. Likewise, use of adjuvant CT was also associated with improved DFS (31.6 vs 18.3m, p < 0.0001), OS (31 vs 18.5m, p < 0.0001), and OS (62 vs 26.5m, p < 0.0001) compared to no CT. The Table below shows 5Y and 10Y survival outcomes by adjuvant treatment received. On multivariate analysis, older age, grade 3 disease, deep myometrial invasion >50%, and no adjuvant RT or CT were identified as adversely impacting RFS, DFS and OS.

Conclusions: In FIGO stage III endometrial cancer patients, use of both CT and RT is associated with improved RFS, DFS and OS and should therefore be recommended in all eligible patients after resection. 54% of patients received both RT, CT and OS are similar across stages IIIA to IIIC2. Risk factors including age, high grade and deep myometrial invasion are independent predictors of survival.

Legal entity responsible for the study: BC Cancer Agency.

Funding: None.

Disclosure: I.J. Ko: Received honorarium from Janssen, Astellas, Bristol-Myers Squib and Merck. Participated in the advisory board for Bristol-Myers Squib, Merck and AstraZeneca. A. Kumar: Participated in advisory boards for Celgene, Roche-Peru, and AmIrene. All other authors have declared no conflicts of interest.

<table>
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<tr>
<td>Survival (RFS (%: p &lt; 0.00001)</td>
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<tr>
<td>5 year</td>
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<tr>
<td>No Tx</td>
</tr>
<tr>
<td>CT</td>
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<td>RT</td>
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<td>Both</td>
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| 977P |
| Is chemotherapy worthwhile in patients with FIGO stage 1b, lymph nodes negative, grade 3 endometrial cancer? |

C. Fontanella 1, G. Legrand 2, A. Barcellini 1, G. Maltese 1, C. Andreetta 2, E. Tripodi 1, F. Martinelli 1, A. Cerutti 1, G. Bogani 1, A. Ditto 1, M. Signorelli 1, C. Scatta 1, C. Sacco 1, F. Raspadelli 1, D. Lorusso 1.

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Background: FIGO stage 1b endometrial cancer represents a major treatment challenge and standard of care is still unclear.

Methods: From March 1996 to March 2016, we retrospectively collected patients diagnosed with endometrial cancer stage Ib (invasion >50% of the myometrium, 2009 FIGO staging), lymph nodes negative after laparadecomy, and grade 3. We performed descriptive analysis and Kaplan Meier test using SPSS 20.0.

Results: Overall, 39 consecutive patients have been collected (28 at the National Cancer Institute of Milan and 11 at the University Hospital of Udine). Median age was 65.8 years (range 53-84.9). Endometrial adenocarcinoma was diagnosed in 32 patients (82.1%), 4 serous adenocarcinoma (10.3%), 2 papillary serous adenocarcinoma (5.1%), and 1 clear cell adenocarcinoma (2.6%). Taking into account only endometrial adenocarcinoma patients received adjuvant chemotherapy (CT) patients (40.6%) received brachyRT; 7 patients (21.8%) received external RT, 2 patients (9.4%) received both; 3 patients underwent platinum-based adjuvant chemotherapy (CT); 7 patients only CT; 2 patients external RT followed by CT and 2 patients brachyRT followed by CT. After a median follow up of 45.8 months (range 27.3-236.8), median disease-free survival was 23.3 months (range 4.7-157.4); 4 patients (21.9%) experienced disease relapse and 5 patients (15.6%) died due to endometrial cancer. Relapse rate was 21.7% in patients who received RT versus 22.2% who did not. To note, relapse rate was only 9.1% in patients who received CT versus 28.6% in patients who did not.

Conclusions: According to our study, patients with stage 1b, node negative, grade 3 endometrial cancer seems to derive a great benefit from adjuvant chemotherapy. This data needs to be further investigated in a large prospective clinical trial.

Legal entity responsible for the study: Department of Gynecologic Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy.

Funding: None.

Disclosure: All authors have declared no conflicts of interest.

| 978P |
| Significance of MSH2 promoter methylation in endometrial cancer with MSH2 deficiency |

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Background: Inactivation of MSH2 was frequently observed in endometrial cancer (EC) with microsatellite instability (MSI) or mismatch repair complex deficiency (dMMR). With respect to MSH2 deficiency (dMSH2), most of dMSH2 were caused by germline mutations in the MSH2 gene or EPICAM deletions. Meanwhile, heritable germline mutations in MSH2 were reported in a few Lynch syndrome families that lacked germline mutations in the MSH2 gene. We previously provided evidence for frequent MSH2 hypermethylation in Lynch syndrome colorectal tumors with dMSH2 and MSH2 methylation may serve as the “second hit” at the wild-type allele. Here, we examined precise epigenetic alteration in MSH2 promoter and tried to reveal associations to family history of Lynch syndrome related tumors.

Methods: We analyzed MSH2 promoter methylation status, as well as MLH1 methylation status, and expression status of the mismatch repair proteins (MLH1, MSH2, PM2S, and MSH6) by immunohistochemistry in 326 EC patients. DNA was extracted from formalin-fixed, paraffin-embedded tissue, and analyzed MSI status by four mononucleotide markers and both MLH1 and MSH2 promoter methylation status by a fluorescent quantitative bisulfite PCR assay.

Results: MSI or dMMR was observed in 82 (25.2%) or 89 ECs (27.3%), respectively. ECs with dMSH2 were observed in 18 (5.5%) of 326 ECs. With respect to MSH2 promoter methylation was detected in 8 tumors (2.5% in 319 tumors excluding not available 7 ECs), and significantly correlated with dMSH2 (P = 0.0072, Fisher’s exact probability test). Then, we also examined the family history of first-degree relatives. In this cohort, although patients with dMMR were significantly associated with family history of Lynch syndrome related tumor (P = 0.0312), patients with this family history were more frequently observed in patients with dMSH2 (P = 0.0052). Interestingly, patients with MSH2 promoter methylation were strongly associated with the family history of Lynch syndrome related tumor (P = 0.0053), though patients with MLH1 methylation were not (P = 0.8345).

Conclusions: MSH2 methylation significantly correlated with ECs with dMSH2 and may have strong relation with family history of Lynch syndrome related tumor, suggesting it plays a role as “second hit” to the MSH2 gene.

Legal entity responsible for the study: Takeshi Nagasaka.

Funding: None.

Disclosure: All authors have declared no conflicts of interest.
Achievement of complete response (CR) in metastatic or recurrent cervical cancer (MRCC): Does it matter?

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1Medical Oncology, Vall d’Hebron University Hospital, Barcelona, Spain, 2Oncología Médica, Hospital Vall d’Hebron, Barcelona, Spain, 3Bioastatistics, Vall d’Hebron Institute of Oncology, Barcelona, Spain, 4Gynaecology, Vall d’Hebron University Hospital, Barcelona, Spain, 5 Radiation Oncology, Vall d’Hebron University Hospital, Barcelona, Spain, 6Pathology, Vall d’Hebron University Hospital, Barcelona, Spain, 7Grupo de Oncology Data Science (CIDyS), Vall d’Hebron Institute of Oncology, Barcelona, Spain

Background: MRCC is a devastating disease with poor long-term outcomes. Bevacizumab (BEV) added to chemotherapy (CT) improves significantly overall survival (OS) in MRCC patients (pts). Aim: to characterize clinic-pathologic features associated to CR and its impact on pts outcome.

Methods: Single-institution chart review of MRCC pts who were treated with 1st line CT between 2005 and 2016. CR was defined by Response Evaluation Criteria in Solid Tumors (RECIST v1). The prognostic and predictive value of clinic-pathologic features, was evaluated.

Results: Seventy-two pts (62% squamous; 30% adenocarcinoma; 8% others); with median age of 48 years (28-77) were selected. Forty-five pts (62%) had prior CT-radiation; 35 pts (79%) had recurrent/persistent disease (27 pts > 12 months disease free interval) and 15 pts (21%) were stage IVA (90% visceral involvement). Moore risk distribution: 7/44/21 pts were high/medium/low risk, respectively. Eleven pts (15%) received BEV + CT, 19 pts (79%) platinum-based-CT (PCT) (54% GpP; 26% Carboplatin) and 4 (6%) non-PCT. After a median follow-up of 33 months, OSR 51.5%, median OS 12 months (95%CI 9.3-NA) and median PFS 6 months (4.6-7.7) were observed for overall population. Moore criteria correlated with prognosis (high-risk pts had significantly worse OS (HR = 0.04, p < 0.001). No differences in ORR, PFS or OS were detected between BEV and non-BEV group (p = 0.2 all comparisons). Higher ORR was observed among low and intermediate risk pts (53%, 67% vs p = 0.006). CRs occurred in 13/17 (76%) evaluable pts (BEV group 2/1, non-BEV 11/60, p = 1). Clinic-pathologic features, including Moore criteria, did not correlate with CR in univariate analysis. Median time of CR was 3.5 months (3-NA) and median duration of CR was 7 months (4.3-NA). Five pts (7%) had CR in the irradiated field. CR significantly impacted on PFS (HR 9.7 vs 4.7 non-CR, p = 0.002) and OS (HR 9.5 vs 9.5 non-CR, p = 0.0001). Eight pts discontinued treatment due to toxicity.

Conclusions: CR is a meaningful surrogate marker for improved PFS and OS in MRCC pts treated with 1st line CT, but no predictive features have been identified in our cohort. Moore prognostic score was validated in real-world practice but its capability guiding therapy needs further evaluation.

Factors Negatively Affecting Voluntary Cervical Cancer Screening Among Educated Indians Above Poverty Line

A. Shukla1, R. Doka2, J.R. Philomen3

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Background: Cervical cancer is the second highest cause of cancer mortality in Indian women with 67,477 reported deaths in 2012 and 83,370 estimated deaths in 2020. Pap smear, an affordable screening test, has shown to reduce mortality by 50 - 80% in various developed countries. However, low cervical cancer screening rate (5.1%) in India has resulted in about 70% of cases being diagnosed at an advanced stage (stage III or IV). The aim of this study is to understand reasons behind lack of voluntary testing among those educated Indians who are above poverty line and who are aware of cervical cancer being a preventable disease.

Methods: We designed a two-part web-based questionnaire containing 18 questions (~90% multiple choice questions). While the first part was designed to capture demographic attributes of the participants, the second part aimed to understand reasons behind low screening levels. The study was distributed between 1st of January 2017 to 30th of April 2017 through social media.

Results: We received a total of 212 responses. After excluding participants who are not currently residing in India or who did not complete the survey, we had 167 evaluable responses. Notably, about 50% (n = 84) of valid participants were aware of cervical cancer, indicating a decent level of awareness among the evaluable population. Among respondents who were aware of cervical cancer, 75% (n = 63) were aware that cervical cancer is preventable by regular screening. However, only 22% of 63 respondents (n = 14) underwent or took their family members for cervical cancer screening. Out of the 49 participants who did not get tested, despite being aware that cervical cancer is preventable, 57% (n = 28) stated time, 18% (n = 9) stated lack of access, and 4% (n = 2) mentioned affordability as a constraint. The remaining 21% gave other reasons most of which are related to the belief that they or their family members have low probability of falling victim to cervical cancer.

Conclusions: Time constraint emerged as the predominant reason for low cervical cancer screening levels among educated Indians who are above poverty line. We propose a proactive approach wherein stakeholders organise well-advertised, easily-accessible screening camps in the residential areas during weekends.

Legal entity responsible for the study: Oncocare Solutions

Funding: Oncocare Solutions

Phase II study of the safety and efficacy of oral capcitabine in patients with platinum-pretreated advanced or recurrent cervical carcinoma

S. Leppö1, C. Fontanella2, G. Maltese3, E. Tripodi4, F. Martinelli5, G. Bogani6, A. Ditto7, M. Signorelli8, C. Scafa9, F. Raspassi9, D. Lorusso10

1Gynecologic Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Background: Cervical cancer is underrepresented in the gynecological clinical research. The objective of this observational study was to evaluate the activity and the safety of capcitabine in patients with platinum-pretreated recurrent cervical carcinoma.

Methods: In this phase II study we enrolled patients with advanced or recurrent cervical carcinoma pretreated with platinum-based therapy. All patients signed an informed consent and were treated at the Gynecological Unit of the IRCCS National Cancer Institute of Milan (Italy). All patients received a starting dose of oral capcitabine 1250 mg/m² twice a day continuously from day 1 to day 14 every 21 days, dose reduction to 1000 mg/m² twice a day was permitted due to adverse events (AE). We used Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 to evaluate response to therapy and Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 to evaluate adverse events. We performed descriptive analysis and Kaplan-Meier test using SPSS 20.0.

Results: From December 2013 to January 2017, we enrolled 20 patients with advanced or recurrent cervical carcinoma, already exposed to platinum, to received oral capcitabine. All patients receive a combination of carboplatin plus paclitaxel as first-line therapy for advanced/recurrent disease. Median age at the first capcitabine administration was 56.9 years (range from 27 to 82 years). After three cycles of oral capcitabine the clinical benefit rate (CBR) was 60.0% (5.0% CR, 30.0% of PR and 25.0% of SD).

No grade 3 or worse severe adverse events were reported. CBR was 88.8% in adenocarcinomas
Background: Vulvar cancer is a rare malignancy in women. During the past 30 years, large surveys of vulvar cancer have not been performed in Japan. We therefore conducted a multicenter study to clarify the clinicopathological features of vulvar cancer in Japan (UMIN000017080).

Methods: In this multicenter retrospective cohort study, the clinical data of patients with vulvar cancer were surveyed. The medical records of patients with vulvar cancer patients treated between 2001 and 2010 were retrospectively reviewed after obtaining approval from the Institutional Review Board of each institution. Survival analysis was performed using Kaplan-Meier curves. The effects of the clinical factors on OS were measured using a Cox regression model.

Results: A total of 1082 patients treated in 108 centers were studied. The median age was 72 years (range, 20 to 96). The disease stage was stage I in 415 patients (38.3%), stage II in 249 (22.3%), stage III in 255 (23.6%), and stage IV in 163 (15.1%) (FIGO 2009). The diagnosis was squamous cell carcinoma in 779 patients (72%), Paget’s disease in 148 (13.6%), adenosquamous carcinoma in 63 (5.8%), and others in 82 (7.6%). Positive lymph nodes were found in 237 patients (21.8%). The median tumor diameter was 35 mm (range, 1.0 to 1.8). The 5-year overall survival was 86% in stage I, 74.7% in stage II, 48.2% in stage III, and 39.9% in stage IV (P < 0.001), and that according to histology was 65.9% in squamous cell carcinoma, 57.1% in adenosquamous carcinoma, 79.7% in Paget’s disease, and 85.8% in others. The hazard ratio was 0.51 in patients with a history of Paget’s disease or others (vs. squamous cell carcinoma or adenosquamous carcinoma; P = 0.001; 95% CI, 0.35–0.75). 2.14 in patients with a number of positive lymph nodes 2 or more (vs. 0 or 1; P < 0.001; 95% CI, 1.50–4.05). 2.10 in patients with a tumor diameter ≥ 35 mm (vs. < 35 mm; P = 0.001; 95% CI, 1.36–3.23).

Conclusions: Treatment outcomes in Japanese patients with vulvar cancer were similar to those reported previously. However, squamous-cell carcinoma, adenosquamous carcinoma, positive lymph nodes, and bulky tumors were associated with poor outcomes. Multidisciplinary treatment might be required in patients with these characteristics.

Clinical trial identification: Registry Name: UMIN Clinical Trials Registry Registration Number: UMIN000017080
Legal entity responsible for the study: No
Funding: None
Disclosure: All authors have declared no conflicts of interest.

Table 98STIP

<table>
<thead>
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<th>Treatment Groups (1:1 randomization)</th>
<th>Concurrent</th>
<th>Maintenance</th>
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<tbody>
<tr>
<td>Primary surgery</td>
<td>C1: Gb + pac + atezo/PL C2: Gb + pac + bev + atezo/PL</td>
<td>C7 onward: bev + atezo/PL</td>
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<tr>
<td>Neo</td>
<td>C1-2 and 5-6: Gb + pac + bev + atezo/PL</td>
<td>C7 onward: bev + atezo/PL</td>
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<td></td>
<td>C3-4: Gb + pac + atezo/PL</td>
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Background: Niraparib (ZELUDA®) is a selective poly (ADP-ribose) polymerase (PARP) 1/2 inhibitor. In preclinical studies, niraparib concentrated in the tumor vs plasma, delivering >90% durable PARP 1/2 inhibition and a persistent antitumor effect. In the ENGOT-OV16/NOVA trial, niraparib demonstrated clinical efficacy in patients with recurrent ovarian cancer (OC) following complete response (CR) or partial response (PR) to platinum-based chemotherapy (PBC) regardless of BRCA mutation or homologous recombination deficiency (HRD) status.

Trial design: The primary objective of the ongoing ENGOT-OV26/PRIMA trial is efficacy (measured as progression-free survival) of niraparib vs placebo in advanced OC patients with CR or PR following frontline PBC. Secondary objectives include overall survival, patient-reported outcomes (PROs), time to first subsequent therapy, time to progression on the next anticancer therapy, and safety and tolerability of niraparib.

Target enrollment is ≥350 patients with stage III or IV OC with PR or CR after PBC. Eligibility criteria include all patients with stage IV disease and patients with stage III disease who were treated with neoadjuvant chemotherapy followed by interval debulking surgery or who have either inoperable disease or visible residual disease after primary debulking surgery. Patients are stratified based on HRD status (HRD positive, including the known deleterious BRCA mutations gBRCAm or sBRCAm/HRD negative), neoadjuvant chemotherapy (yes/no), and best response to PBC (CR/PR).

Patients are randomized 2:1 to oral niraparib 300 mg or matching placebo once daily in 28-day cycles. PRO data will be collected.

Clinical trial identification: NCT02655016

Legal entity responsible for the study: Tesaro, Inc.

Funding: Tesaro, Inc.


A randomized, double-blind, placebo-controlled multicenter phase 3 trial of niraparib maintenance treatment in patients with advanced ovarian cancer following frontline chemotherapy

A. González Martín, I. A. Malinowska, Y. Li, I. A. Malinowska, Y. G. Lin, F. Hoffman, L. Y. Li.

Background: Approximately 18% of patients (pts) with high-grade epithelial ovarian cancer (OC) harbour a deleterious germline BRCA1 or BRCA2 (BRCAl/2) mutation, and 7% harbour a somatic BRCA1/2 mutation (Pennington et al. Clin Cancer Res. 2014;20:764-75). The poly(ADP-ribose) polymerase (PARP) inhibitor rucaparib is approved in the United States for the treatment of pts with deleterious BRCAl/2 mutation (germline and/or somatic) associated advanced OC who have been treated with ≥2 chemotherapy regimens. Data comparing PARP inhibitors to standard of care (SOC) treatment for relapsed OC (regardless of histology) and a deleterious germline or somatic BRCAl/2 mutation who received ≥2 prior chemotherapy regimens. Pts stratified by progression-free interval after their most recent platinum regimen will be randomised 2:1 to receive rucaparib (600 mg BID) (n=230) or chemotherapy (n=115). Pts with platinum-resistant (progressive disease [PD] ≥ 6 months after last platinum) will receive rucaparib or weekly paclitaxel: pts with platinum-sensitive disease (PD > 6 months after last platinum) will receive rucaparib or paclitaxel (37.5 mg/m² weekly) plus platinum-based chemotherapy (single-agent or doublet, per investigator discretion). Pts receiving chemotherapy have the option to cross over to rucaparib upon radiographic disease progression. The primary endpoint is investigator-assessed progression-free survival (RECIST version 1.1). Secondary endpoints include overall survival, objective response rate, RECIST/CAPA-12 response, duration of response, and patient-reported outcomes. Safety will be summarised descriptively using standard adverse event reporting.

Clinical trial identification: EudraCT 2016-000816-14; NCT0285944

Legal entity responsible for the study: Clovis Oncology, Inc.

Funding: Clovis Oncology, Inc.

Disclosure: R.S. Kristeleit: Consulting or advisory role: Clovis Oncology. A. Ouklim: A. Oaknin: A. Milner: Employed as a contractor for AstraZeneca, but does not own stock. All other authors have declared no conflicts of interest.

988TIP

A multicentre phase II study of AZD1775 plus chemotherapy in patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer


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Background: Ovarian cancers have a high rate of mutation in TP53, which produces a G1/S checkpoint deficiency and increases the level of endogenous DNA

Oncology Stock and Other Ownership Interests: Clovis Oncology; C. Unger: Employment: Clovis Oncology Stock and Other Ownership Interests: Clovis Oncology, Sillajen. A.M. Oza: Consulting or Advisory Role: Amgen, Verastem, Clovis Oncology, Immunovaccine Travel, Accommodations, Expenses: AstraZeneca Honoraria. WebRi. All other authors have declared no conflicts of interest.
Key eligibility criteria include platinum resistant OC or fallopian tube/peritoneal cancer (recurrence <6 months; primary refractory excluded); measurable disease per RECIST v1.1; <2 prior lines of therapy; ECOG PS 0-1; and TP53. Approximately 97 pts will be enrolled at 26 global sites from 28 January 2015 with expected study completion in Q2 2018. Pts are restaged every 2 cycles and can continue treatment until progressive disease or unacceptable toxicity. Arms A and D enrolled 9 and 12 pts, respectively. Enrolment in Arm B was initially 8 pts and is now expanded by another 30 pts following emerging data on clinical activity. In Arm C, 6 initial pts were enrolled followed by another 17 pts; a further 12 pts will be enrolled to explore an alternative AZD1775 dosing regimen (see Arm C2 above).

| Table: 990TIP |
|-------------------|-------------------|-------------------|-------------------|-------------------|
| A                 | B                 | C                 | D                 |
| AZD1775          | Chemotherapy      | mirvetuximab      | mirvetuximab      |
| 175mg PO daily    | gemcitabine       | soravtansine      | soravtansine      |
| [D]1-2, 8-9, 15-16 | 1000mg/m² IV D1,8,15 q28D | 175mg PO BID x 5 doses | 225mg PO BID x 5 doses |
| Weekly Days       | paclitaxel 80mg/m² | D1-3, 8-10, 15-17 | D1-3, 8-10, 15-17 |
| 15-16             | IV D1, 8, 15 q28D | carboplatin AUC   | carboplatin AUC   |
|                   |                   | 5 IV D1 q21D      | 5 IV D1 q21D      |
|                   |                   | pegylated liposomal doxorubicin | pegylated liposomal doxorubicin |

| AZD1775          | Chemotherapy      | mirvetuximab      | mirvetuximab      |
| 175mg PO daily    | gemcitabine       | soravtansine      | soravtansine      |
| [D]1-2, 8-9, 15-16 | 1000mg/m² IV D1,8,15 q28D | 175mg PO BID x 5 doses | 225mg PO BID x 5 doses |
| Weekly Days       | paclitaxel 80mg/m² | D1-3, 8-10, 15-17 | D1-3, 8-10, 15-17 |
| 15-16             | IV D1, 8, 15 q28D | carboplatin AUC   | carboplatin AUC   |
|                   |                   | 5 IV D1 q21D      | 5 IV D1 q21D      |
|                   |                   | pegylated liposomal doxorubicin | pegylated liposomal doxorubicin |

225mg PO BID x 5 doses D1-3, 8-10 (+ D15-17 if tolerated) 225mg PO BID x 5 doses D1-3, 8-10 (+ D15-17 if tolerated) 225mg PO BID x 5 doses D1-3, 8-10 (+ D15-17 if tolerated) 225mg PO BID x 5 doses D1-3, 8-10 (+ D15-17 if tolerated)
993TiP Comparing doses and fractionation regimens for high dose rate brachytherapy in locally advanced cervical carcinoma: A randomized controlled trial

A. Manirakiza, F. Rubagumya, D. Msemo, N. Dharsee
Academic Department, Ocean Road Cancer Institute, Dar Es Salaam, Tanzania

Background: Cervical cancer is among the most common gynecologic malignancies encountered in Low and Middle Income Countries. Tanzania, and the whole East African region where it belongs, has cervical cancer as the first malignancy in women, in both incidence and mortality. Despite the advances in management of cervical carcinoma, most of the Low-Income Countries lag in terms of treatment planning and delivery, considering the loads of patients that consult on a regular basis. Locally advanced cervical cancer status, as defined by the International Federation of Gynecology and Obstetrics confers to the patient a high recurrence and low survival rate risks altogether. Survival rates have been shown to have a decreasing tendency as the cancer stage increase. According to FIGO classification, the management of a locally advanced cervical cancer consists of a course of combined radiotherapy and chemotherapy, with a few added weeks of brachytherapy. As it has been shown before, both exposure and toxicity to any of the available treatment options could be lowered if some factors are taken into consideration. Encouraging results have been shown elsewhere. This study compares two different dose fractionations of High dose rate brachytherapy for selected cases of cervical carcinoma, and seeks to prove feasibility of both.

Trial design: The study is an open-label, single institution, non-inferiority, phase 3 randomized controlled trial. Patients will be assigned (1:1), with a consecutive recruitment according to set randomization criteria, to receive two brachytherapy insertions of 8.5 Grays, one week apart (intervention group – A) or three brachytherapy insertions of 6.7 Grays, one week apart (control group – B). Patients will be enrolled then randomized to either group after satisfactory completion of a 5 week-course of both external beam radiotherapy, total dose of 50 Grays, on a 2 Gray daily in 25 fractions, combined with a weekly single agent cisplatin for a dose of 40 mg/m². The study will have a recruitment phase spanning between April to June 2017 and a follow up phase from May 2017 to May 2018.

Legal entity responsible for the study: Muhimbili University of Health and Allied Sciences
Funding: None
Disclosure: All authors have declared no conflicts of interest.
Background: GP2013, a rituximab biosimilar, has been developed according to biosimilar development guidelines, with clinical trials in rheumatoid arthritis and follicular lymphoma (FL).

Methods: This confirmatory phase III, double-blind, randomized, controlled trial compared efficacy, safety, pharmacokinetics (PK) and pharmacodynamics (PD) of GP2013 versus rituximab-CVP (R-CVP) in previously untreated, advanced-stage FL. The primary endpoint was equivalence in overall response rate (ORR), defined by 95% confidence interval (CI) with a margin of ±2%. Secondary endpoints included progression-free survival (PFS), overall survival (OS), 1-year PFS, 1-year OS, and safety. Patients were stratified by region and FLIPI risk score and randomized (1:1) to 8 cycles of treatment, with 28 day cycles of continuous infusion at doses from 3 to 1000 ng/kg/day. During C1W2-4, patients receive the cohort target dose (300-600 ng/kg/day for 4 days). During C1W5-8, patients receive the cohort target dose (300-600 ng/kg/day for 4 days).

Results: The Ph 1 dose-escalation study will define the safety profile, maximum tolerated dose (MTDS), and preliminary anti-leukemic activity of flotetuzumab. Relapsed/refractory (R/R) AML or intermediate-2/high-risk MDS will be treated with 28 day cycles of continuous infusion at doses from 3 to 1000 ng/kg/day. During C1W1, patients receive a lead-in dose (LID) of 30 ng/kg/day for 3 days followed by 100 ng/kg/day for 4 days. During C1W2-4, patients receive the cohort target dose (300-1000 ng/kg/day) on either a 4-day on/3-day off or a continuous 7-day on weekly schedule.

Conclusion: The study demonstrated equivalence in ORR between the biosimilar GP2013 and reference rituximab in patients with previously untreated, advanced FL. Similarity in ORR was observed across subgroups and safety profiles were also comparable. Based on the totality of evidence, GP2013 was approved by the EMA and represents an important option for patients that need rituximab and to help sustain the cost of cancer care.

Clinical trial identification: NCT01419665

Legal entity responsible for the study: Hexal AG, a Sandoz company, part of the Novartis group

Funding: Hexal AG


Background: Acute myeloid leukemia (AML) CD34+...
WDTC had a worse prognosis than patients with AML that occurred spontaneously (P < 0.0001). Finally, patients that were diagnosed with AML after RAI treatment for WDTC diagnoses in case-control studies.

Results: Of 148,215 WDTC patients identified between 1973-2014, 55% received surgery alone and 45% received surgery and RAI. After a median 4.3 person years of follow up (IQR, 1.9-7.4), 44 patients developed AML after surgery alone for WDTC and 56 patients developed AML after surgery and RAI. Compared to the background rates in the general population, patients treated with surgery and RAI had an increased risk of developing AML that peaked within the first three years after RAI treatment (RR: 5.6, 95% CI: 3.8-8.1, P < 0.0001). After correction for sex and WDTC tumor stage (HR: 1.36, 95% CI: 1.09-1.75, P = 0.007) were independent prognostic factors for AML development. WDTC patients that developed AML after surgery and RAI had a truncated survival as compared with matched WDTC control patients that did not develop AML (median OS: 7.5 years vs 24.4 years, P < 0.001). Finally, patients that were diagnosed with AML after RAI treatment for WDTC had a worse prognosis than patients with AML that occurred spontaneously (median OS: 1.2 years vs 3.5 years, P = 0.004).

Conclusions: RAI treatment is associated with an increased risk of developing AML in WDTW survivers. RAI-related AML has a poor survival, similarly to t-AML that arise after radiotherapy or chemotherapy. Considering young patient ages at WDTC diagnosis and high survival rates, the rates of AML in WDTW survivors are likely to continue to rise.

Legal entity responsible for the study: Cleveland Clinic

Funding: American Cancer Society

Disclosure: All authors have declared no conflicts of interest.

997PD

Split dosing of daratumumab (D) in a phase 1b study of D plus carfilzomib (K)-based regimens in patients (pts) with multiple myeloma (MM)


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Background: D, a human CD38 IgG1κ mAb, induces deep, durable responses in pts with relapsed/refractory MM, as monotherapy and combined with other regimens. Infusion-related reactions (IRRs) occur in ~50% of D-treated pts, are generally mild to moderate, and usually occur during the 1st infusion. The median duration of the 1st infusion is ~7 hours. To determine if splitting the first dose would reduce IRRs and infusion-time, split-dose D was evaluated in two K-based regimens (MMY1001: POLLUX, 31 (13%) and 21 pts (7%) received post-infusion medications, respectively. IRRs occurred in 45% and 48% of pts and 98% and 96% of IRs occurred during the first infusion in CASTOR and POLLUX, respectively. All pts were grade 1/2 and no grade 3/4 IRRs were reported.

Table: 997PD

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<tr>
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<th>CD1D</th>
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<tbody>
<tr>
<td>First dose (mg/kg)</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Second dose (mg/kg)</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Maximum rate (mg/hr)</td>
<td>200</td>
<td>200</td>
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<tr>
<td>Total infusion (h)</td>
<td>500</td>
<td>500</td>
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</tbody>
</table>

Clinical trial identification: NCT01998971

Legal entity responsible for the study: Janssen Research & Development, LLC

Funding: Funding provided by Janssen Research & Development


998PD

Management of infusion-related reactions (IRRs) in patients (pts) receiving daratumumab plus standard care of the treatment of multiple myeloma (MM) in the phase 3 studies CASTOR and POLLUX

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Background: Daratumumab (D), a CD38-targeted monoclonal antibody, reduced the risk of MM progression or death by ~70% when combined with standard-of-care regimens in the phase 3 studies CASTOR (bortezomib [V] and daratumumab [D] vs D; NCT02136188) and POLLUX (lenalidomide [R] and D vs D; NCT02076999). This analysis evaluated the management of D-related IRRs in the D and D/R arms of CASTOR and POLLUX.

Methods: Pts had MM and had received ≥1 line of therapy. In CASTOR, pts were given 8-21 day cycles of V-D (V 1.3 mg/m2 subcutaneously on Days 1, 4, 8, and 11; 2.0 mg per os [PO]/intravenously [IV] on Days 1-2, 4, 5, 8, 9, and 11-12) ≥ D (16 mg/kg IVQ for Cycles 1-3, every 3 weeks [Q3W] for Cycles 4-8, then every 4 weeks [Q4W] thereafter). In POLLUX, pts were given 28-day cycles of R (25 mg PO on Days 1-2; 40 mg PO) ≥ D (16 mg/kg IVQ for Cycles 1-2, every 2 weeks for Cycles 3-6, then Q4W thereafter). In addition, pre-infusion medication consisted of 20 mg d (or equivalent) IV/PO; 650-1000 mg paracetamol, and 25-50 mg diphenhydramine (or equivalent). Pts with high-risk respiratory complications received diphenhydramine on Days 1 and 2, a short-acting B2 adrenergic receptor agonist and control medications for lung disease after D infusion.

Results: All pts receiving D were given pre-infusion medication. In CASTOR and POLLUX, 31 (13%) and 21 pts (7%) received post-infusion medications, respectively. In both trials, the median duration of D infusion was ~7.0, 4.3, and ~3.4 hours for the first, second, and subsequent infusions, respectively. IRRs occurred in 45% and 48% of pts and 98% and 96% of IRs occurred during the first infusion in CASTOR and POLLUX, respectively. Most IRs were grade 1/2 and no grade 3/4 IRRs were reported.
Background: Multiple myeloma is a disease of age. With all of the new myeloma drugs being developed, there are a number of treatment options for relapsed and refractory multiple myeloma (RRMM). However, in our knowledge, few data are available in patients older than 65 years of age. We performed a meta-analysis to compare the efficacy of new drugs to treat RRMM between younger and older patients.

Methods: PubMed and the Cochrane databases were searched up to April 2016. We included phase III randomized controlled trials (RCTs) of monoclonal antibodies (mAbs) targeting CD38 or SLAMF7 (daratumumab, elotuzumab), second generation proteasome inhibitors (carfilzomib, ixazomib) and histone deacetylase (HDAC) inhibitors (vorinostat, panobinostat) reporting subgroups comparison of progression-free survival (PFS) based on aged cut-offs. The summary hazard ratio (HR) and 95% confidence interval (CI) were calculated.

Results: A total of 5241 patients from eight RCTs of RRMM new therapies were included (CASTOR, POLLUX, ELOQUENT-2, ASPIRE, ENDEAVOR, 1UCOG, Hopital Rene´ Muret APHP, Sevran, France, 2He´matologie Centre Recherche Clinique, AP-HP Hoˆpital Avicenne, Bobigny, France, 3Geriatric Oncology, AP-HP Hoˆpital Renel Muret, Sevran, France).

Conclusion: Multiple myeloma is a disease of age. With the new treatments being developed, we need more data to compare the efficacy of new drugs to treat RRMM between younger and older patients.
Background: Copaniib, a novel class I PI3K inhibitor with predominant activity against α and δ isoforms, has shown robust single agent anti-tumor activity in a phase 2 study in heavily pretreated patients with indolent NHL (iNHL) and follicular lymphoma (FL) (NCT01660451; Part B), with response rates of 39.6% and 58.7%, respectively. Baseline tumor gene expression profiling (GEP) was performed to confirm if gene signatures identified in patients with indolent or aggressive NHL (NCT01660451; Part A) are molecular determinants for copaniib antitumor activity in Part B.

Methods: Signaling pathway gene sets (n = 35) were ranked by enrichment analysis (COSA) for association with objective response based on normalized enrichment score (NES) and false discovery rate (FDR) q values. The association of weighted gene-expression score (WGS, reflecting the overall expression level for each gene set) with response was assessed by logistic regression.

Results: Seventy-one patients with iNHL, including 54 FL, had both response data and evaluable gene expression data. All 5 gene sets reflecting upregulated PI3K/BCR signaling were top-ranked for association with higher response rates in iNHL (GSEA NES ≥ 1.93, FDR q < 0.01; WGS AUC ≥ 0.65, nominal p < 0.04) and FL (GSEA NES ≥ 1.50, FDR q < 0.01; WGS AUC ≥ 0.60, nominal p < 0.25). Among patients with objective responses, 66% (33/47) of iNHLs and 71% (24/36) of FLs had high PI3K/BCR gene signature expression levels, for patients with CR, 86% (47/55) iNHL and 84% (3/3) FL had high levels. Further, 4 gene sets enriched with T-cell signatures were associated positively with copaniib response (NES > 1.48, FDR q < 0.01). In contrast, up-regulation of macrophage/stromal gene sets was potentially associated with a lower likelihood of response to copaniib treatment in FL (NES = -1.21, q ≤ 0.21).

Conclusions: Tumor gene expression profiling demonstrates that up-regulation of the BCR/PI3K pathway is frequent and dominant in iNHL and FL, and is associated with the high and durable copaniib responses. These findings are consistent with copaniib’s mode of action and strongly support the rationale for treatment of iNHL and FL patients with copaniib.

Clinical trial identification: NCT01660451; Part B
Legal entity responsible for the study: Bayer AG
Funding: Bayer AG

1004PD
Tumor gene expression signatures of BCR/PI3K dependence in association with copaniib monotherapy activity in heavily pretreated patients with indolent NHL and follicular lymphoma

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Background: There are few studies that analyse follicular lymphoma (FL) mortality compared to the general population of the same-sex and age group. Given the recent clinical relevance of the predictive event-free survival (EFS) indices EFS12 and EFS24, we obtained them in our study cohort in order to estimate their association with overall survival (OS).

Methods: Patients diagnosed with FL were prospectively enrolled from 1980 to 2013. Standardized mortality ratios (SMR) were obtained using yearly sex and age specific mortality rates in Spain, and OS was compared with age- and sex-matched general population data. EFS were defined as the time from diagnosis until relapse or progression, unplanned retreatment of lymphoma after initial management, or death due to any cause. EFS12 and 24 were defined as EFS status at 12 or 24 months from diagnosis, respectively. The crude probability of death was estimated by using the Kaplan–Meier method, and differences between patient groups were assessed by the log-rank test. In order to investigate the specific contribution of age, sex, period of diagnosis, treatment and FLIPI score, a multivariable Cox proportional hazards model was adjusted. All statistical tests were two-sided, and a p-value < 0.05 was considered statistically significant.

Results: A total of 1074 patients with newly diagnosed FL were enrolled. The median OS was 251 months (CI 95% 195–267). EFS at 12 and 24 months was associated with increased probability of early death, with an SMR of 10.27 (95% CI: 8.26–12.77). The prognostic value of traditional scales such as FLIPI is maintained in our study, with a hazard ratio of 2.7 (95% CI: 1.9–4.0) for a score of 2–5. Of note, no significant difference in mortality was observed between FL patients at 10 years since diagnosis compared to the general population (SMR of 1.02; 95% CI 0.37–1.85).

Conclusions: EFS12 and 24 predicted an earlier increase in mortality. The long-term SMR, over 10 years of follow-up, shows that patients with FL have a similar risk of dying than the general population of the same sex and age.

Legal entity responsible for the study: GOTEL (Spanish Lymphoma Oncology Group)
Funding: None
Disclosure: All authors have declared no conflicts of interest.

1003PD
A multicentre phase II trial addressing lenalidomide (LEN) maintenance in patients with relapsed diffuse large b-cell lymphoma (DLBCL) who are not eligible for autologous stem cell transplantation (ASCT)

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Background: Single-drug maintenance after salvage therapy could prolong survival of pts with DLBCL not eligible to ASCT. LEN could be an excellent candidate as its oral agent, active against DLBCL, with excellent safety profile. Herein, we report results of a multicentre phase II trial addressing LEN maintenance (mLEN) in pts with chemosensitive DLBCL.

Methods: HIV-negative pts with DLBCL relapsed after R-CHOP or similar and responsive to salvage therapy were registered and treated with LEN 25 mg/day for 21 days out of 28 until lymphoma failure or unacceptable toxicity. Primary endpoint was the 1-year PFS. Estimated sample size (Simon’s two-stage optimal design; type I error 5%, power 80%, 80% P0 30%, P1 50%) was 47 pts; mLEN would be considered effective if ≥ 19 pts will be progression-free survivors at 1 year. The prognostic role of cell of origin, assessed by NanoString and Hans algorithm, was investigated.

Results: 46 of 48 enrolled pts were assessable (median age 72 years; 34:46; 26 pts started mLEN in CR and 20 in PR after salvage therapy; 639 LEN courses were delivered, with an average of 14 courses/pt (3-53). LEN was well tolerated: with the exception of neutropenia, grade 3-4 toxicities were uncommon (<5% of courses). LEN dose reduction was indicated in 25 pts. Three pts died of toxicity: intestinal infarction, meningitis, unknown cause; 2 pts developed sepsis. The two pre-determined efficacy threshold (n ≥ 19) was largely achieved: 32 pts were progression free at 1 year from registration. At a median follow-up of 38 (14-95) months, 23 events occurred: PD in 19 pts, death due to toxicity in 3, death while off therapy in 1, with a 1-yr PFS of 70% (95%CI:59–81). The benefit of mLEN was observed both in pts with de novo or transformed DLBCL, and both in GCB- or non-GCB-DLBCL (29 · 63% are alive, with a 3-yr OS of 64%).

Conclusions: With the limitations of a non-randomized design, this trial soundly promotes the use of LEN in pts with chemosensitive DLBCL not eligible for ASCT or experiencing relapse after ASCT. These results warrant further investigation of immunomodulatory drugs as maintenance in these high-risk pts.

Clinical trial identification: NCT00799513
Legal entity responsible for the study: IRCCS San Raffaele
Funding: None
Disclosure: All authors have declared no conflicts of interest.

1004PD
Follicular lymphoma: clinical and molecular characteristics of histologic transformation

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Background: FoliCal lymphoma (FL) is the second most common type of non-Hodgkin lymphoma (NHL). Histological transformation (HT) refers to the evolution of
of a clinically indolent NHL to an aggressive one. The rates of HT in published series range from 10% to 60%. There are no specific clinical characteristics that can predict transformation. Some molecular parameters associated with transformation are: p53 expression, expression of c-MYC, BCL-6 mutations. This suggests that multiple alternative mechanisms are likely to be involved in the pathogenesis of HT.

Methods: We report a prospective, multicenter (39 Spanish member institutions of Grupo Oncológico para Tratamiento de Linfomas-GOTEL-), observational study designed to collect data on disease presentation, treatment and clinical outcomes of HT. Inclusion criteria for this analysis were initial diagnosis of grade 1-3A FL and enrollment from 1998 to 2016. HT was defined as refractory/recurrent disease with clinical or pathologic diagnosis. Whole exome sequencing of the HT samples has been performed and compared with samples from patients with LF without transformation.

Results: Of the 975 evaluable patients, 64 had HT. Characteristics associated with an increased risk of HT were: the presence of 8 symptoms (p = 0.001), increased LDH (p = 0.02), high Follicular Lymphoma International Prognostic Index (FLIPI) (p = 0.01) and poor performance status (p = 0.01). In this group of patients, the cumulative incidence rate of HT at 5 years was 7.3%; the rate of HT remained constant, reaching a plateau after 14 years. Expectant management also predicted for a higher risk of HT (p = 0.001). The median survival from transformation was 5 years. Regarding molecular characteristics, we found that all patients with HT had more than 4 mutations at diagnosis of FL in a group of 14 genes that are frequently mutated in patients with HT: CSMD3, DTX1, FOXO1, ERPB1, NOTCH2, PIM1, POL222, ATM, BCL7A, HIST1H1E, IRF8, PCLO, EZH2 and TNAIP3.

Conclusions: There are clinical (increased LDH, 8 symptoms, high FLIPI, poor performance status) and molecular factors (more than 4 mutations in specific genes) at diagnosis correlate with an increased risk of HT. These predictors of HT could help to develop targeted therapies to prevent HT in high risk patients or improve current salvage approaches.

Legal entity responsible for the study: GOTEL (Grupo Oncológico para el Tratamiento y Estudio de Linfomas)

Funding: None

Disclosure: All authors have declared no conflicts of interest.

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### Table: 1005PD Multivariate analysis of 783 patients in the primary cohort

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<tr>
<th>Covariate</th>
<th>level</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
<th>nomogram score</th>
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<tbody>
<tr>
<td>Age</td>
<td>&gt;60y</td>
<td>1.32</td>
<td>1.02-1.72</td>
<td>0.036</td>
<td>28</td>
</tr>
<tr>
<td>≤60y</td>
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<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>ECOG PS score</td>
<td>≥2</td>
<td>1.84</td>
<td>1.38-2.44</td>
<td>&lt;0.001</td>
<td>62</td>
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<tr>
<td>0 or 1</td>
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<tr>
<td>LDH</td>
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<td>1.64</td>
<td>1.27-2.12</td>
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<td>Ann Arbor stage</td>
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<td>1.81-3.99</td>
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<td>100</td>
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<td>Stage I</td>
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<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Stage II</td>
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<td>1.25</td>
<td>0.86-1.84</td>
<td>0.247</td>
<td>23</td>
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<tr>
<td>Ki67 index</td>
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<td>1.73</td>
<td>1.30-2.29</td>
<td>&lt;0.001</td>
<td>56</td>
</tr>
<tr>
<td>&lt;90%</td>
<td></td>
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<tr>
<td>CD5 express</td>
<td>Positive</td>
<td>2.35</td>
<td>1.56-3.54</td>
<td>&lt;0.001</td>
<td>87</td>
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<tr>
<td>Negative</td>
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<td>BCL6 express</td>
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<td>0.55-0.95</td>
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</table>

Conclusions: The proposed nomogram provides an individualized risk estimate of OS in patients with DLBCL, especially for the patient who received R-CHOP like regimen.

Clinical trial identification: This project was approved by the Ethics Committee of Cancer Hospital, Chinese Academy of Medical Sciences.

Legal entity responsible for the study: National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College

Funding: None

Disclosure: All authors have declared no conflicts of interest.

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### Table: 1006PD

<table>
<thead>
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<th>PFS</th>
<th>OS</th>
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<tr>
<td>Hazard ratio (95% CI)</td>
<td>Hazard ratio (95% CI)</td>
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<tr>
<td>P value</td>
<td>P value</td>
</tr>
</tbody>
</table>

#### Age

| Age ≥ 60 | Not included | 1.94 (1.09-3.48) | 0.025 |
| Treatment* | Not included | 1.76 (0.90-3.43) | 0.096 |
| PS ≥ 2 | 1.62 (0.74-3.57) | 0.235 | 1.77 (0.84-3.74) | 0.134 |
| Stage > 2 | 2.04 (1.01-4.00) | 0.047 | 1.59 (0.98-2.88) | 0.127 |
| IPI > 2 | 1.33 (0.70-2.50) | 0.385 | 1.14 (0.60-2.17) | 0.686 |
| LDH > ULN | 1.09 (0.63-1.89) | 0.778 | 1.03 (0.63-1.69) | 0.893 |
| Burkitt* | 1.30 (0.81-2.10) | 0.283 | 1.58 (1.03-2.42) | 0.037 |
| Oncorcin omission* | 1.21 (0.76-1.95) | 0.421 | 1.12 (0.75-1.69) | 0.571 |
| Extramedullary ≥ 1 | 1.02 (0.59-1.78) | 0.932 | Not included |
| Kidney/Adrenal* | 1.72 (0.78-3.85) | 0.171 | 2.45 (1.20-4.98) | 0.014 |
| BM ≥ 25 | 0.89 (0.58-1.37) | 0.591 | 0.98 (0.67-1.43) | 0.904 |
| Doxorubicin ≤ 70% | 1.88 (0.97-3.67) | 0.063 | 2.04 (1.15-3.57) | 0.014 |

Conclusions: Does the omission of vincristine affect outcome and survival in patients with diffuse large B-cell lymphoma?

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2Upsala University, Department of Immunology, Genetics and Pathology, Uppsala, Sweden

Background: The current standard treatment for diffuse large B-cell lymphoma (DLBCL) is Rituximab-CHOP (cyclophosphamide (CPI), doxorubicin (DXR), vincristine (VCR), prednisolone). It is well known that VCR causes peripheral neuropathy and is often dose-reduced or omitted from the treatment. Whether the omission of VCR from 1 or more cycles of therapy could jeopardize the survival of patients with DLBCL has not yet been adequately addressed. Our study aimed to investigate any differences in progression free (PFS) and overall (OS) survival in R-CHOP treated patients with DLBCL between those with omission of VCR or not.

| Table: 1006PD |
|--------------|---------------|
| PFS | OS |
| Hazard ratio (95% CI) | Risk ratio (95% CI) |
| P value | P value |

#### Age

| Age ≥ 60 | Not included | 1.94 (1.09-3.48) | 0.025 |
| Treatment* | Not included | 1.76 (0.90-3.43) | 0.096 |
| PS ≥ 2 | 1.62 (0.74-3.57) | 0.235 | 1.77 (0.84-3.74) | 0.134 |
| Stage > 2 | 2.04 (1.01-4.00) | 0.047 | 1.59 (0.98-2.88) | 0.127 |
| IPI > 2 | 1.33 (0.70-2.50) | 0.385 | 1.14 (0.60-2.17) | 0.686 |
| LDH > ULN | 1.09 (0.63-1.89) | 0.778 | 1.03 (0.63-1.69) | 0.893 |
| Burkitt* | 1.30 (0.81-2.10) | 0.283 | 1.58 (1.03-2.42) | 0.037 |
| Oncorcin omission* | 1.21 (0.76-1.95) | 0.421 | 1.12 (0.75-1.69) | 0.571 |
| Extramedullary ≥ 1 | 1.02 (0.59-1.78) | 0.932 | Not included |
| Kidney/Adrenal* | 1.72 (0.78-3.85) | 0.171 | 2.45 (1.20-4.98) | 0.014 |
| BM ≥ 25 | 0.89 (0.58-1.37) | 0.591 | 0.98 (0.67-1.43) | 0.904 |
| Doxorubicin ≤ 70% | 1.88 (0.97-3.67) | 0.063 | 2.04 (1.15-3.57) | 0.014 |
Methods: In this Swedish multi-institutional, retrospective cohort study we included all adult patients diagnosed with and primarily treated for DLBCL or subgroups of high-grade malignant B-cell lymphoma with either R-CHOP/CHOP (CHOP plus Etoposide) or mini-CHOP (dose-reduced), between 2000-2013. All information on patients’ characteristics, treatment outcome, and survival was extracted from the in-hospital computer based systems. Any clinical variables significantly associated with PFS or OS in univariate analysis by the log-rank test were considered for entry into a multivariate Cox proportional hazard regression model. Omission of VCR was included in all models as an independent variable of interest. All statistical analyses were performed with IBM SPSS statistics version 22.

Results: In total 541 patients were included in the study cohort. In 95 (17.6%) patients, VCR was omitted due to toxicity. The omission was more often decided during the last 3 cycles of chemotherapy (86 patients, 90.5%). Univariate analysis revealed 9 potential prognostic factors associated with PFS and 10 with OS. Omission of VCR was not associated with either PFS or OS in both univariate and multivariate analyses (HR for PFS: L.21, 95% Confidence Interval (CI) 0.76-1.95; HR for OS: 1.12, 95% CI 0.75-1.69). For PFS only advanced stage at diagnosis was found to be significantly associated with worse outcome (p = 0.047). In respect of OS kidney/adrenal involvement (p = 0.014), Doxorubicin –Relative Dose Intensity<-0.70 (p = 0.014), age ≥60 years (p = 0.025) and bulky disease (p = 0.037) were significant predictors of survival.

Conclusions: Omission of VCR does not affect either PFS or OS in patients with DLBCL treated with CHOP-like chemotherapy. Omission of VCR in case of severe neurotoxicity due to VCR. Considering the association of bulky disease and kidney/adrenal manifestation of lymphoma on survival, further studies should focus on whether the treatment in these subgroups need to be individualized. Finally, clinicians should be aware of the importance of giving adequate dose of DXR during treatment given the growing body of evidence on the role of dose intensity on survival.

Legal entity responsible for the study: Stockholm University

Disclosure: All authors have declared no conflicts of interest.

Clinical trial identification: NCT02632540

Legal entity responsible for the study: Karolinska University Hospital, Stockholm

Funding: None

Disclosure: None

ZUMA-4 preliminary results: phase 1 study of TCR-ALL genetically engineered CAR T cell therapy for patients with relapsed/refractory acute lymphoblastic leukemia (R/R ALL)


Background: Outcomes for adult pts with R/R ALL are poor. Promising results were observed with axi-cel (KTE-C19), an anti-CD19 chimeric antigen receptor (CAR) T cell therapy, in B cell malignancies (Locke et al. ACRR 2017, #9986). Severe cytokine release adverse events (NE) and neurologic events (NE) have been observed in pts with R/R ALL who received anti-CD19 CAR T cell therapy.

Methods: Eligible pts were aged ≥18 years with R/R ALL (Pt + pts eligible), >50% bone marrow (BM) lymphoma, ECOG status 0-1, and adequate organ function. Pts received 1 or 2 low-dose conditioning (cyclophosphamide/fludarabine). Phase 1 primary endpoint was incidence of dose-limiting toxicity (DLT). Secondary endpoints were efficacy outcomes.

Results: As of Dec 31, 2016, 4 of 5 enrolled pts have been treated; median follow-up, 5.3 mos (1.9-8.6). All pts had ≥2 prior lines of therapy and 1 pt had prior stem cell transplant (SCT). All pts received bridging chemotherapy due to high disease burden (base-line blasts, 41.99%) prior to KTE-C19. KTE-C19 was successfully manufactured in a centralized 6-7 d process across a range of baseline absolute lymphocyte counts (0.5-17.1 x 10^9/L) and CD4/CD8 ratios (0.1-0.7). KTE-C19 could not be manufactured for 1 pt who progressed with WBC >150,000/uL at apheresis and <0.2% T cells in the apheresis collection. There were no DLTs. One pt had a grade 3 AE due to intracranial hemorrhage from disseminated mucormycosis. All pts had cytokine release syndrome (CRS) grade 1 or 2, or grade 3 or 4 with full-field eye examination and no organ failure. No pts had cytokine release syndrome (CRS) grade 3 or 4 with partial/incomplete hematologic recovery; 1 blast-free hypoplastic/aplastic BM). Median follow-up was 3.8 mos; 3 pts relapsed: 2 CD19+ and 1 CD19+ disease. Efficacy was similar across KTE-C19 doses. To refine dosing and AE management, additional pts were treated with lower CAR T cell doses and received prophylactic tocilizumab. Clinical outcomes and translational data from these pts will be presented.

Conclusions: KTE-C19 demonstrates promising efficacy with a manageable safety profile for adult R/R ALL pts. Novel approaches to reducing toxicity, namely CRS and NE, may improve the overall risk: benefit profile for this class of therapies.

Clinical trial identification: NCT02632540

Legal entity responsible for the study: Kite Pharma

Funding: Kite Pharma


ZUMA-4 1007PD Preliminary results of novel safety interventions in adult patients (pts) with relapsed/refractory acute lymphoblastic leukemia (R/R ALL) in the ZUMA-3 Trial


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Background: Outcomes for adult pts with R/R ALL are poor. Promising results were observed with axi-cel (KTE-C19), an anti-CD19 chimeric antigen receptor (CAR) T cell therapy, in B cell malignancies (Locke et al. ACRR 2017, #9986). We present preliminary ZUMA-4 phase 1 results.

Methods: Pts aged ≥21 y with R/R ALL and adequate organ function received the planned dose of 1 or 2 x 10^6 CAR T cells after conditioning (cylophosphamide/fludarabine). Phase 1 primary endpoint is the incidence of DLTs. Secondary endpoints include efficacy and biomarker assessments.

Results: As of 31 Dec, 2016, 4 of 5 enrolled pts have been treated; median follow-up, 5.3 mos (1.9-8.6). All pts had ≥2 prior lines of therapy and 1 pt had prior stem cell transplant (SCT). All pts received bridging chemotherapy due to high disease burden (base-line blasts, 41.99%) prior to KTE-C19. KTE-C19 was successfully manufactured in a centralized 6-7 d process across a range of baseline absolute lymphocyte counts (0.5-17.1 x 10^9/L) and CD4/CD8 ratios (0.1-0.7). KTE-C19 could not be manufactured for 1 pt who progressed with WBC >150,000/uL at apheresis and <0.2% T cells in the apheresis collection. There were no DLTs. One pt had a grade 5 AE due to intracranial hemorrhage from disseminated mucormycosis. All pts had cytokine release syndrome (CRS) grade 1 or 2, or grade 3 or 4 with full-field eye examination and no organ failure. No pts had cytokine release syndrome (CRS) grade 3 or 4 with partial/incomplete hematologic recovery; 1 blast-free hypoplastic/aplastic BM). Median follow-up was 3.8 mos; 3 pts relapsed: 2 CD19+ and 1 CD19+ disease. Efficacy was similar across KTE-C19 doses. To refine dosing and AE management, additional pts were treated with lower CAR T cell doses and received prophylactic tocilizumab. Clinical outcomes and translational data from these pts will be presented.

Conclusions: KTE-C19 after low-dose CyFlu was tolerable and appears safe for further analysis in pediatric and adolescent pts with R/R ALL. KTE-C19 can induce deep remissions in heavily pre-treated pts with high disease burden. Based on these results, ZUMA-4 continues to enroll (NCT02625480).

Clinical trial identification: NCT02625480

Legal entity responsible for the study: Kite Pharma

Funding: Kite Pharma

Annals of Oncology

Pharmaceuticals to conduct this study. R. Fram: Consultant for Takeda Employee at Xcenda, a healthcare consulting firm that received funding from Takeda Takeda Pharmaceuticals. E. Farrelly, M. Pollack, A. Raju, A. Ogbonnaya, M. Eaddy:

Disclosure:

Funding:

erly AML population.

search is needed to evaluate other factors in therapy selection and prognosis for the eld-

were male, and 19.1% had a Charlson comorbidity index score of

Results: 1704 eligible AML pts, 398 received ILT. Mean age was 70.6 years, 55.5% were male, and 19% had a Charlson comorbidity index score of ≥ 2. ILT regimens included cytarabine-based induction ILT (C-IC) in 54.3% (n = 216, combined with an anthracycline [e, 7 or 3 + 7 + 3-LRC] in 87.5% of these), hypomethylating agents (HMAs) (azacitidine and decitabine) in 30.2% (n = 110), other cytotoxic IC (other-IC) in 8.5% (n = 34), and sorafenib in 1.0% (n = 4). 44 pts (11.1%) had record of stem cell transplant during 1LT for AML. A higher proportion of pts who received HMAs

(EHS24) have a very good prognosis. We need to perform an accurate follow up with pa-
tients in the first 2 years after diagnosis to detect early relapses and focus on studying the molecular biology of these tumours to detect differences in relapsed patients. Follow up after 5 years from diagnosis will detect only a small account of relapses and probably will not make an impact on survival.

Legal entity responsible for the study: Hospital Puerta de Hierro Majadahonda Funding: None

Disclosure: All authors have declared no conflicts of interest.

101P

Interpreting progression-free survival and overall survival data in biosimilar clinical studies: considerations based on a recent rituximab biosimilar study

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Background: Oncology trials often report data on progression-free survival (PFS) or overall survival (OS), but such endpoints are prone to be less sensitive than short-term overall response (ORR) for confirming biosimilarity when long median PFS or OS are expected. We outline considerations when interpreting survival data with a sensitivity analysis from a recent rituximab biosimilar study

Methods: A confirmatory phase III study compared the efficacy of the EMA approved biosimilar rituximab, GP2013 (n = 314) with reference rituximab (R) (n = 315) in pa-
tients with previously untreated, advanced follicular lymphoma. Patient is given rCHP chemotherapy during induction and responders received GP2013 or R maintenance monotherapy. Primary endpoint was equivalence of ORR at the end of induction. Secondary endpoints included PFS and OS, and hazard ratios (HRs) were estimated by a Cox proportional hazard model, with treatment allocation as the main effect and FLIPI strata as a stratification factor.

Results: As of 31 Dec 2016, the median follow-up was 23.6 and 24.2 months for GP2013 and R, respectively. Equivalent criteria for the primary endpoint were met, confirming biosimilarity. For time-dependent endpoints, there was a high level of censoring without PFS (<79%) or OS (<90%) events. Median PFS or OS could not be esti-

ated. HRs for PFS and OS were 1.31 (90% CI [1.02–1.69]) and 0.77 (90% CI [0.49, 1.22]), respectively. Kaplan-Meiur analysis showed that PFS survival curves diverged between 12–24 months yet ran parallel outside this period, violating the proportional hazards assumption of the Cox proportional hazard model. Complete response (CR) rates were similar between treatments at all time points, including 33 months.

Conclusions: Small sample size, low event rate, data immaturity and/or other aspects of study design can subject survival analyses to chance findings and decrease sensitivity for biosimilarity assessments. In this study, HRs for PFS and OS had opposite direc-
tions and CR rates between treatments were similar across time, emphasizing these challenges. The PFS and OS results should be interpreted with caution as they may not reflect a difference, or lack thereof, between treatments.

Clinical trial identification: NC731419665

Legal entity responsible for the study: Hexal AG, a Sandzco company, part of the Novartis group

Funding: Hexal AG, a Sandzco company, part of the Novartis group

Disclosure: J. Amersdorfer: Employee of Hexal AG, Holzkirchen, Germany. Y. Li, S. Alexandrova: Employee of Sandzco Inc. Princeton, NJ, USA. A. Zubel, E. Sasse: Employee of Hexal AG, Holzkirchen, Germany. H. Mellstedt: Received speaker or con-
sultancy honoraria from: F. Hoffmann-La Roche Ltd, Amgen Inc.; Pfizer Inc.; Hospira; Boehringer Ingelheim Pharmaceuticals, Inc.; AbbVie Inc., Sandzco.

Role of prephase treatment prior to definitive chemotherapy in diffuse large B cell lymphoma (DLBCL)

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Background: Treatment related toxicity during the treatment of Diffuse large B cell lymphoma (DLBCL) is highest during the initial phase of treatment (First cycle effect). The toxicity can be fibule neutropenia, tumour lysis syndrome, deterioration in performance status and death. Introduction of prephase treatment is popular method to reduce this toxicity. This study was undertaken to evaluate the benefit of prephase treat-

ment in Indian patients.

Methods: This was a prospective study carried out at Kidwai memorial institute of oncology, Bangladesh, India from July 2013 to December 2016. The newly diagnosed patients of DLBCL, age >18years, stage II-IV were enrolled in study. Written consent taken from all patients before starting chemotherapy (CHOP-R-CHOP). Of 30 patients, 25 patients received prephase treatment consisting of vincristine (1 mg) on

6th days and prednisone 100 mg daily for 7 days (6-day to day 0). All patients received CHOP-R-CHOP chemotherapy on day 1. ECOG performance status, nadir absolute neutro-

phil count (ANC) on day 10, fibule neutropenia, and hospitalization, requirement of

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doi:10.1093/annonc/mdx373 | 361
antibiotics and mortality within 30 days of chemotherapy were compared in both the groups. Patients above 60 years received prophylactic growth factor.

Results: The median age of the patients were as 50.5 years (Range 20-74 years). Thirty patients were male and twenty patients were female. Twenty patients (40%) had stage 2 disease while remaining 69% patients had stage 3 or stage 4 disease. Most of the patients (96%) attained ECOG performance status of 0 or 1 after prephase treatment. The incidence of any grade neutropenia on D10 of chemotherapy in experimental arm was 48% (95%CI 34-62) while the grade 3/4 neutropenia was 12% (48% in control arm). Febrile neutropenia in the experimental arm was lower (12%) compared to control arm (32%) (p value<0.05). The mortality within 30 days remains same (4%), in both the arms.

Conclusions: Prephase treatment significantly improves the performance status of DLBCL patients prior to receiving chemotherapy (CHOP-R rituximab). First cycle effect, including decrease chances of febrile neutropenia and improvement in nadir ANC are impressive benefits of prephase treatment.

Legal entity responsible for the study: Kidwai memorial institute of oncology, Bengaluru India

Funding: None

Disclosure: All authors have declared no conflicts of interest.

<table>
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<th>1013P</th>
<th>The role of FDG-PET/CT in detecting bone marrow involvement in diffuse large B-cell lymphoma</th>
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<tr>
<td>A. Bulbul1, E.A. Mino1, S. Choua1, A. Bautista1, A. Mustafa1, H. Abboud1, S. Rashad1, T. Braik1, K. Mansouf1</td>
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</table>
1Hematology/Oncology, Kymera Independent Physicians, Carlsbad, NM, USA, 2Anesthesiology, Ashaya Shi Chander College of Medical Sciences and Hospital, Jammu, India, 3Medicine, Windsor University, Meetei, IL, USA, 4Medicine, All Saints University of Medicine, Rowena, Dominica

Background: The sensitivity and prognostic value of FDG-PET/CT in the staging of Diffuse Large B-Cell lymphoma (DLBCL) remain unclear. PET/CT provides a high level of accuracy for identifying focal skeletal marrow disease in Hodgkin’s lymphoma (HL). Whether the omission of staging Bone Marrow Biopsy (BMB) would change or not.

Methods: We retrospectively studied 114 patients with DLBCL from three rural community oncology practices in New Mexico between January 96- September 2016. Patients receiving RMB and PET/CT were included. Descriptive statistics and Chi-square methods were used to evaluate associations.

Results: Mean age at diagnosis was 66 years (23-92), 54% were males, 82% received RCHOP therapy. Out of 114 patients, 27 (23%) patients did not have a staging BM biopsy. The sensitivity of PET/CT scan was 73% and Specificity 87%. Positive predictive value (PPV) 50% and Negative predictive value (NPV) 95%. Patients with positive focal PET/CT were more likely (50% vs 5%) to have a positive BMB in comparison those with negative PET/CT scan. There was correlation with BM involvement

Conclusions: PET/CT is valuable as having a high negative predictive value for detection of focal marrow involvement in DLBCL. This may help avoid BM biopsy, especially in early stage disease. Cytopения did not predict marrow involvement. The long-term prognostic value of PET/CT is similar to that obtained by a bone marrow biopsy.

Legal entity responsible for the study: Kymera Independent Physicians

Funding: None

Disclosure: All authors have declared no conflicts of interest.

<table>
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<th>1014P</th>
<th>Evaluation of various prognostic scores and impact of cell of origin on survival in limited stage DLBCL: retrospective study</th>
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<tr>
<td>M.S. Badil1, S. Askhar1, T. Ahmed1, E. Hassan2, Q. Shafik3, F. A. Almugbel1, M. N. Zahir1, N. Badit1, I. Maghrbi1</td>
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</table>
1Medical Oncology, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

Background: Utility of International Prognostic Index (IPI) as standard prognostic tool in limited stage diffuse large B-cell lymphoma (Li DLBCL) has been controversial. Variety of other prognostic scores have been proposed including Miller’s stage modified IPI (M-IPI), NCCN-IPI (N-IPI), and stage adjusted IPI (Sa-IPI). We aimed to compare various prognostic scores. In addition, data is not clear regarding impact of cell of origin (COO) i.e. Germinal Center (GC) and non-GCB COO in patients with Li DLBCL. Our aim is to identify difference in survival outcomes by COO.

Methods: All patients with newly diagnosed non-bulky Li DLBCL treated with standard first line CHOP-R chemotherapy with or without radiation from 1987 to 2013 were eligible. Discrimination ability of each prognostic model was also tested using bagging model. Model performance was evaluated using sensitivity, accuracy and Area under the Receiver Operating Characteristic Curve (AUC) and model which scored highest AUC, was selected. Survival times and survival proportions were estimated using the Kaplan-Meier survival curves. In addition, we applied Hans’s algorithm to study prognostic impact of COO.

Results: The median age of the 276 included patients was 47 years. 32% received limited chemotherapy (36% in control arm) while 68% patients received extended chemotherapy. The median follow up was 4.9 years. M-IPI was the best prognostic indicator of both DFS (AUC=0.67) and OS (AUC=0.72) when compared with IPI, N-IPI and St-IPI.

Disclosure: All authors have declared no conflicts of interest.

Table: 1014P Comparison of prognostic models for Li DLBCL

<table>
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<th>Risk model</th>
<th>Sensitivity</th>
<th>F-statistical</th>
<th>AUC</th>
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<tr>
<td>St-IPI</td>
<td>0.92</td>
<td>0.91</td>
<td>0.69</td>
</tr>
<tr>
<td>IPI</td>
<td>0.47</td>
<td>0.51</td>
<td>0.57</td>
</tr>
<tr>
<td>N-IPI</td>
<td>0.81</td>
<td>0.84</td>
<td>0.66</td>
</tr>
<tr>
<td>M-IPI</td>
<td>0.73</td>
<td>0.6</td>
<td>0.68</td>
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</table>

Conclusions: Our data identified that in limited stage non-bulky DLBCL, M-IPI is more robust tool for outcome prediction with better power for risk stratification in the CHOP-R as compare to other prognostic models. There was no statistically significant difference in DFS or OS for patients in the GCB and non-GCB limited stage non-bulky DLBCL.

Legal entity responsible for the study: Oncology Center, King Faisal Specialist Hospital and Research Center

Funding: None

Disclosure: All authors have declared no conflicts of interest.

<table>
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<th>1015P</th>
<th>The prognostic impact of serum albumin and absolute neutrophil count in patients with newly diagnosed diffuse large B-cell lymphoma</th>
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<tr>
<td>B. Spassov1, D. Yassileva1, G. Arnaudov1, S. Nikolov1, G. Mihaylov1, G. Balatzenko1, M. Guemova1</td>
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</table>
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Background: Patients (pts) with diffuse large B cell lymphoma (DLBCL) are treated with immunochemotherapy and are generally stratified by the NCCN International prognostic index (N-IPI). It has been reported that some host-related factors such as nutritional status (NS) and systemic inflammation (SI) were associated with the outcome of pts with solid tumors. However, data regarding their prognostic contribution in DLBCL are limited. Therefore, we decided to access the possible prognostic significance of some laboratory markers associated with NS/SI in DLBCL pts.

Methods: We retrospectively reviewed the clinical outcome of 251 R-CHOP treated DLBCL pts. A receiver operating characteristic (ROC) curve analysis was used to illustrate the best cut off values of the serum albumin (SA), beta-2-microglobulin, absolute neutrophil (ANC), lymphocyte, monocyte and platelet counts, and hemoglobin level to predict overall survival (OS) by Kaplan-Meier method in our data set.

Results: The estimated 5-year OS of the whole group was 61%. The multivariate analysis showed that only SA and ANC remained independent predictors of OS by applying the best cut off values determined by ROC: 39.4 g/L and 5.3 x 10^9/L, respectively. Furthermore, the combination of dichotomized SA and ANC generated a prognostic index (SA/ANC-PI) that stratified patients into 3 different risk groups: low risk (LR) (SA < 39.4 g/L and ANC and 5.3 x 10^9/L) (intermediate risk IR) (SA > 39.4 g/L or ANC < 5.3 x 10^9/L) and high risk HR (SA > 39.4 g/L and ANC > 5.3 x 10^9/L). The 5-year OS for LR, IR and HR pts was 86%, 65.7% and 22.5% (P < 0.001), respectively, and our PI was independent of the NCCN-IPI.

Conclusions: Our data showed that SA/ANC-PI could predict OS in DLBCL pts and may present a reliable, convenient and sensitive predictor to identify pts with poor prognosis in addition to NCCN-IPI.

Legal entity responsible for the study: Specialized Hospital for Active Therapy of Hematological Diseases

Funding: None

Disclosure: All authors have declared no conflicts of interest.
High-dose chemotherapy followed by ASCT is a widely used treatment for aggressive or recurrent NHL for young patients (pts). Limited data are available on the feasibility and the results of this strategy for older pts, who are often excluded from aggressive treatment. This study aimed at comparing pts >65 years old (70% pts) to a younger pts’ population in terms of tolerance, safety and results of ASCT.

Methods: We did a retrospective study in one center in France. We included every consecutive pts treated by ASCT for NHL from May 2007 to January 2016. We collected data on the characteristics of the pts and their disease, previous treatments, and tolerability and outcome after ASCT.

Results: 48 pts > 65 yo (mean: 49.5) and 129 < 65 yo (mean: 68.7) at the time of the transplant were included. The most common histology was diffuse large B cell lymphoma (p = 0.205). There were only 2 differences between the 2 groups. First, the number of pts with comorbidities was higher in the elderly population (p = 0.016), especially cardiovascular (p < 0.001). Secondly, the moment of the ASCT was mainly on first line for young pts vs at the time of relapse for older pts (p < 0.001). At the time of ASCT, in both groups (p = 0.306), a majority of patients were in complete response. No differences were found between the 2 groups for the conditioning regimen, number of CD34+ cells, number of transfusion, weight loss, length of the hospital stay and duration of aplasia. There were no differences of grade ≥ 3 toxicities (hematologic, infections, digestive, renal, cardiac, mucositis) for both groups (p = 0.116).

Treatment Related Mortality (death within 30 days following ASCT) was 2% for pts >65yo vs 3.9% (p = 1). The mean follow-up time was 36 months for young pts vs 77 months for older (p = 0.001). The specific survival was similar between the 2 groups, 65% for the young pts group vs 72% for the older (p = 0.63) 3 years after ASCT.

Conclusions: High-dose chemotherapy followed by ASCT is as safe and effective in a population of pts >65 yo compared to a younger population. Aggressive treatment could be considered earlier in the management of elderly pts and should not be excluded only depending on the age of the patient.

Legal entity responsible for the study: Centre Antoine Lacassagne

Disclosure: All authors have declared no conflicts of interest.

Phenotypic and functional characterization of tumor infiltrating lymphocytes (TIL) generated from non-hodgkin lymphoma tumors: Implications for the development of novel therapies for lymphoma

BACKGROUND: TIL are generated from leukapheresis in patients undergoing ASCT. TIL products can be centrally manufactured for broad clinical application. Adoptive cell therapy with TIL involves collection of autologous lymphocytes from the tumor via surgical resection, ex vivo expansion of TIL lymphodepletion of the patient prior to infusion of TIL, follow by infusion of TIL and treatment with IL-2. Here, we present findings related to expanding TIL directly from lymphoma.

METHODS: Using methods for TIL isolation and growth developed at Lion, we expanded TIL from 9/5 lymphomas (1 MCL, 3 follicular, 1 DLBCL) with Interleukin 2 for 11-14 days and subsequent rapid expansion for 14 days using mitogenic anti-CD3 antibody and irradiated allogeneic PBMC.

RESULTS: TIL were generated from all 5 lymphoma tumors with a maximum expansion index of 600-fold, significantly higher than previously reported. Mean CD3+ T-cell population was 95% (vs 75% previously reported). As with TIL expansion from melanoma, we observed a marked relative increase in effector memory cells in lymphoma TIL. A significant increase in TEMRA (p < 0.001; CD4+, CD8+) and CD68+CD4+ (p = 0.008) subsets was observed in lymphoma compared with melanoma TIL. A broad repertoire of known melanoma antigens, NY-ESO-1, MART1 and MAGEA4 were highly expressed in lymphoma TIL. No loss of TIL reactivity upon expansion in lymphoma TIL.

CONCLUSIONS: We demonstrate here the feasibility of growing TIL from lymphoma that can be considered earlier in the management of elderly pts and should not be excluded only depending on the age of the patient.
High expression level of IL13 could be considered as a negative prognostic marker. In multivariate analysis, high levels of calcium and LDH, status performance and 1021P Evaluation of the PI3K pathway in peripheral T-cell lymphoma

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1Division of Medical Oncology, National Cancer Centre Singapore, Singapore, 2Division of Clinical Trials and Epidemiological Sciences, National Cancer Centre Singapore, Singapore, 3Single Health Tissue Repository and Advanced Molecular Pathology Laboratory, Singapore Health Services, Singapore, 4TRG-Oncology, Bayer AG, Berlin, Germany

Background: Peripheral T-cell lymphomas (PTCL) are a heterogeneous group of aggressive malignancies with dismal outcomes and limited treatment options. While the PI3K pathway has been shown to be activated in many B-cell lymphomas, its therapeutic relevance in PTCL is not clear. The aim of this study was to investigate the expression and activation of the signaling molecules in the PI3K pathway in each subtype of PTCL and to identify the potential therapeutic options for clinical testing.

Methods: The expression of PI3Ka, PI3Kβ, PI3Kγ, Akt1, pAkt1 and PTEN was analyzed in 88 PTCL samples by immunohistochemistry. This included all major mature T- and NK-cell neoplasms. Univar- iate and multivariate analyses were also performed using the expression and patients’ clinical data.

Results: Staining for PI3Kα and Akt1 was positive in 86 (98%), PI3Kβ in 85 (97%), PI3Kγ in 79 (90%), PI3Kδ in 50 (57%) and pAkt1 in 45 (51%) samples. No PTEN staining was observed in 9 (10%) cases and the expression was weak in 70 (80%) samples. There were no correlations between expression and PTCL subtype. Patients with high pAkt1 had higher IPI score (P = 0.004) and higher stage (P = 0.02). Loss and low expression of PTEN were associated with older age at diagnosis (P = 0.02). In the univariate analysis, high PI3Kδ, older age, high IPI and high ECOC score were significantly associated with inferior OS and DFS (P < 0.05). In addition, low PI3Kδ (in contrast to PI3Kα), male gender and elevated LDH were also associated with worse PFS (P < 0.05). The median OS of patients with low PI3Kα was 25 months (95% CI 14.8–67.0 months) compared to 11 months (95% CI 1.8–16.3 months) in patients with high PI3Kα.

Conclusions: All 88 samples demonstrated at least partial activation of the PI3K pathway. High PI3Kα expression was an independent poor prognostic factor for both OS and PFS. This study provides evidence that PI3Kα and PI3Kδ pathways, particularly inhibition of PI3Kδ, could be a promising approach for the treatment of PTCL.

Legal entity responsible for the study: Choon Kiat Ong

Funding: Bayer AG

Disclosure: O. Politz, N. Liu: Employee of Bayer AG. C.K. Ong: Received research funding from Bayer AG. All other authors have declared no conflicts of interest.

1021P Safety and tolerability of chemotherapy (CT) containing high doses of methotrexate (HD-MTX) and cytarabine ( Ara-C) in patients with primary central nervous system lymphoma (PCNSL) and hepatitis B virus (HBV) infection

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Background: HBV reactivation is a serious complication of some anticancer therapies. Preliminary studies suggested high rates of HBV reactivation, with fatal outcome, in pts with PCNSL treated with standard HD-MTX-based CT. Risk of HBV reactivation is further increased by the use of rituximab (Rtx), which significantly improves efficacy of CT in PCNSL. Hence, HBV-positive pts are usually excluded from prospective trials, with a negative effect on accrual, and are treated with less intensive therapies, resulting in lower cure rates. Herein, we report the incidence of HBV infection and reactivation in 85 pts treated with different regimens in our institution. Methods: HBV-negative pts with newly diagnosed PCNSL treated with CT containing HD-MTX and Ara-C were evaluated. Results: 48 pts (median age 58, range 29–76) were included. Eight (17%) pts had resolved HBV infection (negative HBsAg but positive anti-surface [anti-HBs] or anti-core [anti-HBc] Antibodies), one (2%) pt had active infection. HBV prophylaxis with lamivudine was indicated in 3/8 pts with resolved HBV. The pt with active infection was treated with entecavir. Induction comprised HD-MTX plus Ara-C in 2 pts, HD-MTX, Ara-C and Rtx in 2, and HD-MTX, Ara-C, thiorexa and Rtx in 5 (MATRix). Transient grade 1–2 elevation of hepatic enzymes (AST, ALT, GGT) was observed in all pts; grade 3–4 was recorded in 17/39 (44%) HBV-negative pts and in 5/9 (56%) HBV-positive pts (Fisher exact; p = 0.31). Eight out of 9 HBV-positive pts received the 4 planned CT courses without dose reductions due to hepatotoxicity; six pts achieved a CR and received consolidation (WBRIT 2, ASCT 3, lenalidomide maintenance 1). At a median follow-up of 27 months for the whole series (12–80), no previously experienced HBV reactivation during first-line treatment, 5 pts remain relapse-free.

Conclusions: This study suggests that MTX-Ara-C-based therapy, MATRix regimen, in particular, can be safely used in PCNSL pts with HBV infection, without impaired life expectancy.

Legal entity responsible for the study: IRCCS San Raffaele

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Evaluation of safety, tolerability and efficacy of temsirolimus in patients (pts) with relapsed or refractory mantle cell lymphoma (rel/ relf MCL) in routine clinical practice

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Background: Temsirolimus (TEM), an mTOR inhibitor, is approved in the EU for the treatment of pts with relapsed/refr MCL. A pivotal study demonstrated significantly longer progression free survival (PFS) with TEM (175 mg weekly for 3 weeks followed by 75 mg weekly) in rel/ref MCL pts compared to investigators choice therapy (4.8 vs 1.9 months [mos]; P = 0.009). To evaluate the safety profile and efficacy of TEM in this rare tumor entity, further data collection in an unsolicited routine clinical patient population is useful.

Methods: A German multicenter registry for rel/ref MCL pts treated with TEM was started in Germany in 2009 in cooperation with regulatory and ethics committees approval. Objectives are the evaluation of the safety profile, tolerability and anti-tumor activity of TEM as well as patient’s profile including comorbidities, characteristics, and the sequence of systemic therapies.

Results: From Oct 2009 to Feb 2017, 55 pts were recruited in 30 study sites. Baseline characteristics are available for 55 pts: 69% male; median age 74.4 years; bone marrow involvement in 38.2% of the pts; ECOG PS (n = 54) 0 in 83.3%, ECOG PS 2 in 16.7%. According to MIPD score (n = 53), 20.8%, 34.0%, and 45.2% are classified as low, intermediate, and high risk at the time of enrollment. Median number of prior therapies is 2 with 43.6% treated in ≥ 4th line. Most common drug-related toxicities of any grade (incidence > 15%) are observed in following categories: blood/lymphatic system disorders (49.1%), gastrointestinal disorders (27.3%), general disorders (21.8%), and skin/subcutaneous tissue disorders (18.2%). Efficacy analyses are available for 39 assessable pts with an objective response in 30.8%, a clinical benefit (CR, PR, SD, MR and PD) in 50.0% and PD in 41.0% of the pts. Median PFS for all pts is 3.6 mos. For the subgroup of pts treated with TEM in 2nd and 3rd line PFS is 3.3 mos for ≥ 4th line pts 4.9 mos.

Conclusions: The registry was started to evaluate the safety and efficacy of TEM in pts with rel/ref MCL in routine clinical practice. In this comparatively poor-prognosis patient population, TEM showed a predictable, manageable tolerability profile. Efficacy parameters were consistent with published phase III data.

Clinical trial identification: NCT00700258

Legal entity responsible for the study: Pfizer Pharma GmbH
Funding: Pfizer Pharma GmbH

Endoscopic evaluation of acute intestinal GVHD after allogeneic hematopoietic cell transplantation

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Background: Acute graft versus host disease (GVHD) is a common complication of hematopoietic cell transplantation (HCT). The exact incidence is unknown due to the difficulties in diagnosis. The gastrointestinal tract (GIT) is one of the main target organs in patients with acute GVHD. There is also lack of consensus regarding whether upper or lower GI endoscopy is required first and the site with highest sensitivity for biopsy.

Methods: All patients (111) with suspected intestinal GVHD were evaluated with upper GIS endoscopy or both upper and lower GIS endoscopy according to presenting symptoms. Biopsies were stained using hematoxylin-eosin and evaluated by the same experienced pathologist. The presence of apoptotic bodies, crypt glandular abscesses and crypt glandular destruction was considered confirmatory findings in histologic specimen for the diagnosis of GVHD. And the criteria proposed by Washington were used for histological grading of acute intestinal GVHD.

Results: All patients, HCT was performed on 111 patients of whom 27 (24.3%) had developed acute GVHD. Nineteen of the 111 patients with intestinal symptoms were evaluated for intestinal involvement, and 17 were diagnosed with acute intestinal GVHD. Upper endoscopic findings had a sensitivity of 64.2%, a specificity of 50%, a positive predictive value of 91.6% and a negative predictive value of 14.2%. The diagnostic accuracy of upper endoscopy was 63.1%. Lower endoscopic findings had a sensitivity of 40% and a specificity of 0%. The diagnostic accuracy of upper endoscopy with duodenal biopsy and sigmoidoscopy was 94.3%.

Conclusions: Endoscopic findings are nonspecific in acute intestinal GVHD. There is little agreement between endoscopic findings and histopathology; thus, biopsies are
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Background: Colonie neutropenia remains one of the major concerns of intensive chemotherapy and contributes significantly to morbidity, health care expenditure and mortality. Colonization of gut by MDR bacteria is regarded as a potential risk factor for subsequent infection with the same organism during febrile neutropenia. In this study, we aim to find the profile of surveillance stool culture and its association with febrile neutropenia in patients of acute leukemia undergoing induction chemotherapy.

Methods: Newly diagnosed patients of acute leukemia eligible for intensive chemotherapy were recruited for the study. Baseline stool microscopy and culture sensitivity were done to identify colonization with pathogenic bacteria. Blood and other samples were collected during febrile neutropenia. Association between surveillance stool culture and subsequent infections was studied.

Results: A total of 106 patients were recruited from November 2015 to March 2017. 59 patients were pediatric AL with median age of 10 years and 47 patients were adult AL with median age of 33 years. 68.86% of patients had gut colonization with bacteria of which, 33.01% were MDR while 55.84% were non-MDR. Most common MDR bacteria colonizing gut was E. Coli (62.16%) and Klebsiella Pneumonia (21.82%). A total of 264 blood cultures were taken from 68 patients who developed 114 episodes FN during induction. In patients with positive blood cultures, the incidence of infection was 23.68% non MDR colonizers. Infection mortality was 20% in MDR colonizers compared to 10.32% in non-colonizers.

Conclusions: Our study suggests that a significant proportion of patients are colonized with MDR bacteria and there is a high prevalence of MDR sepsis during induction. MDR sepsis and induction mortality were higher in patients colonized with MDR bacteria compared to non MDR bacteria.

Legal entity responsible for the study: JIPMER

Funding: JIPMER

Disclosure: All authors have declared no conflicts of interest.

1028P L-arginine – targeted for the anthracycline cardiotoxicity prevention in patients with acute leukemia of high cardiological risk

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Background: The risk of anthracycline cardiotoxicity (AC) significantly increases in patients with comorbid ischemic heart disease (IHD), which requires monitoring and prevention during chemotherapy (CT) of acute leukemia (AL). In this study we aim to evaluate the effectiveness of L-arginine in AC prevention in AL patients with comorbid IHD during induction CT.

Methods: A total 66 patients with newly diagnosed AL and comorbid IHD were included in the study. ECOG-0-II. The cohort consisted of 34 (51.5%) males and 32 (48.5%) females, median age 54-72 years. The IHD duration was 3–15 years. CT included doxorubicin. We determined the level of troponin I, nitrite anions [NO2]–, performed daily ECG-monitoring: at baseline and in achieving a cumulative dose of anthracyclines (CTA) from 100 to 200 mg/m2. Depending on AC prevention patients were divided into two groups: I (n = 36) – AL patients treated with CT; II (n = 30) – AL patients treated with CT and L-arginine.

Results: Prior to CT, according to the daily ECG-monitoring in 47 (71.2%) patients’ periods of tachycardia were diagnosed, with single supraventricular extrasystoles (SVS) and ventricular extrasystoles (VES) – in 33 (53%) and 17 (25.7%) pts, respectively. The decreased concentration of [NO2]– in blood serum in 1.5 times relative to normal values (p < 0.05) was noticed. Troponin I in all patients of both groups was < 0.5 ng/ml. Reaching low CDA in group I we recorded: periods of tachycardia in 36 (100%) pts, increasing number of single and paired SVSs – in 24 (66.6%), VEs episodes – in 19 (52%), clinical symptoms of myocardial infarction – in 29 (80.5%) and interval QT prolongation – in 14 (38.8%) pts. Troponin I was > 0.5 ng/ml in 7 (19.4%) pts. Simultaneously, deepening of endothelial dysfunction (ED) was noted: [NO2]– was in 1.8 times lower vs norm. After 2 CT courses in 20 (66.6%) patients of group I on tachycardia background the single SVS were recorded and only in 1 (3.3%) patient troponin I level was > 0.5 ng/ml. The ED levelled: [NO2]– didn’t significantly differ from the norm. The effectiveness of ED in AL patients with comorbid IHD during induction CT leads to the reducing risk of necrotic injury of cardiomyocytes and improves endothelial function that prevents early AC.

Legal entity responsible for the study: Ukrainian Medical Stomatological Academy

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1029P Multiple myeloma complicated by concomitant cardiac pathology

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Background: Patients with multiple myeloma (MM) often have cardiac comorbidities because of several factors, including the history of cardiac events, myeloma and treatment-related factors. Age is an important risk factor, given that the median age at the diagnosis of MM in Russia is 64 years. Additionally, the MM-related cardiac risk factors include underlying and undiagnosed cardiac amyloidosis, hypertensive, high-output failure, anemia and renal failure. Therefore, there are poorly understood mechanisms for the development of the real efficiency anti-myeloma treatment for this category of patients. In the presented work we have analyzed the efficacy of the most commonly used bortezomib-containing regimens in anti-myeloma treatment for patients with MM and concomitant cardiac diseases.

Methods: One hundred and forty-eight (males – 69, females – 79) patients were enrolled in this trial during March 2008 – May 2010. They divided on groups with (1) newly diagnosed and (2) relapsed and refractory MM. The median ages for patients of all groups was 64.7 years (ranges, 36.3 – 82.7). An obligatory condition was the presence in all patients of significant cardiac pathology. The bortezomib-containing regimens VCD (n = 95), VMP (n = 36) or VD (n = 15) were used as anti-myeloma treatments. IWG (2006) criteria were used for anti-myeloma response assessment. Comparisons for categorical variables among different groups were made with chi-square test. Overall survival (OS) was measured from the date of the last follow-up until the date of death or the date of last follow up. For multivariable analysis, factors associated with time to event were introduced into a Cox proportional model.

Results: EOCG performance status of ≤ 2 have 81 (54.7%) patients. The verified diagnosis of ischemic heart disease was in 109 (73.6%) patients and symptoms of chronic heart failure was in 86 (58.1%) patients. The overall response rate (ORR) documented in 65.7% cases with newly diagnosed and 39.5% cases with relapsed and refractory MM including complete and strong complete remission (CR/sCR) in 22.9% and 20.3% cases respectively. With a median follow-up of 4.9 years for the comparison groups, the 5-year overall survival (OS) was 22.8 ± 5.3% and 17.3 ± 4.4% (p = 0.295). The median OS was 40.0 and 31.8 months respectively.

Conclusions: In multivariate analysis only EOCG scores ≥ 2 were demonstrated an independent negative prognostic value both for the event-free survival (Hazard ratio 1.69; p = 0.086) and OS (Hazard ratio 1.76; p = 0.038). Overall, the bortezomib-based treatment in myeloma patients with concomitant cardiac pathology accompanied by no significant increase in the incidence of cardiovascular adverse events.

Legal entity responsible for the study: Pirogov Russian National Research Medical University (RNRMU) Research Medical University (RNRMU)

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1030P Evaluation of dose intensification of cytarabine in postremission therapy in older AML patients within the prospective phase II AMLSG 06-04 study


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Background: Progress in the treatment of acute myeloid leukemia (AML) in older patients (pts) is still limited. In the randomized part of the AMLSG 06-04 trial, valproic acid (VPA) was evaluated in combination with intensive therapy plus all-trans retinoic acid (ATRA). There was a suggestion of a survival benefit for high-dose cytarabine (HDA) in the ATRA + VPA arm. In the present study, we evaluate whether dose intensification of cytarabine (HDA 200 mg/m2 day 7 and 8 followed by HDA 300 mg/m2 days 15-17) in postremission therapy further improves the outcome of older AML patients.
Background: A substantial proportion of chronic myeloid leukemia (CML) patients in deep molecular response (DMR) reach treatment-free remission (TFR) after tyrosine kinase inhibitors (TKI) cessation. The aim of this study is to identify a gene signature predictive for TFR using whole transcriptome expression analyses.

Methods: RNA from peripheral blood (PB) leukocytes of 60 CML patients who stopped TKI therapy within the EUROSKI study and 10 healthy controls were isolated. CML patients were divided into two groups of whom n = 30 patients had ongoing TFR, while 30 patients encountered molecular recurrences. RNA was isolated at the last day of TKI intake. In order to investigate differentially expressed genes, whole transcriptome arrays (Clariom D, Affymetrix) were analyzed. Candidate biomarkers were tested in multivariate analyses and gene set enrichment analyses (GSEA).

Results: CML patients in DMR compared to healthy controls showed 16000 differentially expressed genes (p < 0.05). The natural killer cell marker CD56 showed overexpression with high fold change (> 8-fold) for CML patients versus healthy controls. Significant enrichment of TCR and TGFβ pathways (FDR < 7%) was found in CML patients. Comparing the CML versus TKI relapse cohort, we found 2600 differentially expressed genes. Most notably the toll-like receptors TLR1, TLR6 and TLR8 were upregulated in the relapse cohort (p < 0.05). Activated downstream signatures of NFKB-like; TLR and TNF pathways, known for their pro-motivation of a protective CML microenvironment, were significantly enriched (p < 0.03, FDR < 25%). In contrast, patients in TFR were characterized by upregulation of T-cell receptor and granulocyte gene family members (p < 0.03). Genes of interest showed distinct cut-off predictive for TFR over a period of 12 months.

Conclusions: CML patients in DMR present a considerable inflammatory gene expression pattern in PB leukocytes in contrast to healthy controls. Alike previous studies, genes involved in immune exhaustion and immune surveillance were differentially expressed between patients with TFR and relapse. The specific inflammatory gene signature of the relapse cohort suggests ‘stenness’ as third mechanism and driver for relapse.

Legal entity responsible for the study: University Heidelberg

Funding: EKN Foundation

Disclosure: R. Sebti: Novartis research fund. S. Saussele: Advisory board: Novartis, Bristol-Myers Squib, Pfizer and ARIAID Fees: Novartis, Bristol-Myers Squib, Pfizer and ARIAD Research grant: Novartis and Bristol-Myers Squib Travel grant: Novartis and Bristol-Myers Squib. All other authors have declared no conflicts of interest.

1032P Pharmacodynamic and pharmacokinetic evaluation of SY-1425 (tamibarotene) in biomarker-selected acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) patients

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Background: SY-1425 (tamibarotene) is an oral, potent and selective synthetic RAα receptor agonist previously approved for the treatment of relapsed/refractory acute promyelocytic leukemia (APL) in Japan. Given preclinical evidence of SY-1425 sensitive AML cell line and patient samples with ARA-RARα pathway activation defined by elevated RARA or IRF8, SY-1425 is being investigated in a Phase 2 study of biomarker selected non-APL AML and MDS patients. DHRS3 is a direct RARα target gene with rapid and robust mRNA upregulation in both AML blasts and PBMCs in response to SY-1425. Here we present the first report of SY-1425 plasma levels with DHRS3 based evidence of RARα target engagement from AML and MDS patients enrolled in the Phase 2 study (NCT02807558).

Methods: Patients positive for RARA pathway biomarkers (RARA, IRF8, or both) initiated oral daily treatment with SY-1425 at 6 mg/m2/day in two divided doses. Sparse PK was collected twice on day 1 and twice on day 15. PD was sampled before the first dose and at 5–8 hours post dose on day 1 and once on day 15. DHRS3 expression was assessed by qPCR in PBMCs.

Results: PK: data in 16 patients showed SY-1425 plasma levels were consistent with those observed in Japanese APL patients based on day 1 Cmax and day 15 steady state exposure. In 19 PD evaluable patients, upregulation of DHRS3 at 3–8 hours had a greater than 2-fold increase in 84% (16/19). Induction was consistent for AML and MDS, including patients positive for RARA, IRF8, or both biomarkers. DHRS3 expression remained elevated after 15 days of continuous treatment in evaluable patients. Using a parallel exploratory ex vivo flow cytometry assay from screening samples, SY-1425 induced differentiation and blast reduction that was correlated with biomarker status.

Conclusions: In a biomarker-selected AML and MDS patients with evidence of RARA pathway activation, SY-1425 causes strong transcriptional upregulation of the DHRS3 target gene, consistent with SY-1425 induced differentiation through myeloid gene activation. The dosing regimen of SY-1425 achieves plasma exposures sufficient to elicit a PD response with direct evidence of RARα target engagement.

Clinical trial identification: NCT02807558 received by on June 13, 2016

Legal entity responsible for the study: Syros Pharmaceuticals

Funding: Syros Pharmaceuticals

Disclosure: J. Jurcic: Research funding from Syros Pharmaceuticals, Astellas Pharma, Daiichi Sankyo, Actinium Pharmaceuticals, Forma Therapeutics, Genetech, Celgene, Kuver Oncology. Advisor to Novartis. D. Babii: Consultant for Abbvie, Novartis, Pfizer, Spectrum, Teva; speakers’ bureau for Incyte, Celgene, Gilead, Seattle Genetics. J. Cortes: Research support from Syros Pharmaceuticals. R. Redner: Research funding from Bristol-Myers Squib. Stock or other ownership from Merck, Glaxo, INJ, MDT, BBH. G. Roboz: Advisory & funding: Agios, Astex, Celgene, CTI, MedImmune, MEI, Novartis, Onconova, Pfizer, Celestics; funding: Abbvie, Karyopharm, Moffitt, Tenax; Advisory: Amphivena, AstraZeneca, Boehringer, GSK, Janssen, Roche, Shire, Amgen, Celator, Genoptix, juin, Sunesis. M. McKeown, N. Waters, K. Stephens: Employee and stock holder of Syros. E. di Tomaso: Employee and stock holder from Syros Pharmaceuticals. D. A. Roth: Employee and stock holder of Syros Pharmaceuticals. E. Stein: Consulting for Agios, Pfizer, Celgene; research funding from Agios, Celgene, GSK, Seattle Genetics, Syros. All other authors have declared no conflicts of interest.
Background: InO is a humanized CD22-targeted antibody conjugated to N-acetyl-
GlcNAc copolymer chemotherapy. In a phase 2 study comparing single-agent InO with 3IC, the goal of this analysis was to quantify differences in response for the endpoints complete response (CR/CRi) with incomplete hematologic recovery (CRi) and minimal residual disease-negative (MRD (-)) for patients treated with InO relative to 3IC.

Methods: The efficacy endpoints analyzed were CR/CRi per investigator’s assessment and MRD (-). The modeling analyses were performed using generalized bionomial logistic regression, which allows constructing a linear continuous predictor for probabilities of response ranging from 0%–100%. 2 treatment arms were considered: single-agent InO or 3IC (fludarabine, cytarabine, granulocyte colony-stimulating factor, cytarabine with mitoxantrone, or high-dose cytarabine). Additional potential predictors of re-
sponse (eg, baseline demographic/patient characteristics, laboratory values) were also tested.

Results: For the CR/CRi efficacy endpoint, only 3 variables were statistically significant predictors of achieving CR/CRi: treatment arm, baseline ECOG (BECOG) performance status, and baseline absolute blasts in peripheral blood (BLSTABL). For the MRD (-) endpoint, 5 variables were statistically significant predictors of achieving MRD (--): treatment arm, BECOG performance status, baseline cytogenetic characteristics, prior hematopoietic stem cell transplant before study therapy, and BLSTABL.

Conclusions: The odds of achieving CR/CRi and MRD (-) with InO were approxi-
ately 7 and 13 times higher, respectively, than 3IC.

Clinical trial identification: NCT01363297, NCT01564784
Legal entity responsible for the study: Pfizer Inc
Funding: Pfizer Inc
Disclosure: A. Ruiz-Garcia, E. Vandendriessche: Employee of and owns stocks in Pfizer Inc. D.J. DeAngelo: Served on advisory boards for Pfizer Inc. H.M. Kantarjian: Received re-
lated to investigator’s choice of chemotherapy (ICC) in adults with hematologic malignancies Volume 28 | Supplement 5 | September 2017

Table 1: 1033P

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<th>Endpoint, n (%)</th>
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<th>INO-VATE ICC (n = 143)</th>
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*When CR/CRi was not achieved and MRD was missing, MRD was considered not achieved.
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diphendiamine, and an optional leukotriene inhibitor) and patients with a higher risk of respiratory complications will receive post-infusion medications (including diphendiamine, a short-acting β2 adrenergic receptor agonist, and lung disease control medications). Safety evaluations will occur weekly during Cycles 1-2, every 2 weeks during Cycles 3-6, and monthly thereafter. Disease evaluations will occur monthly. The primary endpoint is progression-free survival. Secondary endpoints include safety, overall response rate, minimal-residual-disease-negative rate, duration of response, and overall survival. Approximately 302 patients will be enrolled across 10 countries.

Clinical trial identification: Eudraactr: 2017-001681-27

Legal entity responsible for the study: Janssen Research & Development, LLC

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Background: Data is a monoclonal anti-CD38 antibody approved for the treatment of relapsed and refractory MM. Addition of data to bortezomib and dexamethasone increased complete and overall response rates and improved progression-free survival (PFS) in pts who received data. CyBorD is a bortezomib-based regimen which has been shown to be an effective therapy for MM. This study was designed to evaluate the combination of Data-CyBorD in pts with MM who are previously untreated or have relapsed MM following only one line of prior therapy.

Trial design: This is a multicenter, single-arm, open label, Phase 2 study in pts with MM who have received ≤1 line of prior therapy. Approximately 100 pts (≥40 with untreated MM and ≤40 with relapsed MM) will receive Data-CyBorD every 28 days for 4 to 8 cycles. Pts receive oral cyclophosphamide 300 mg/m2 on Days 1, 8, 15, and 22; subcutaneous bortezomib 1.5 mg/m2 on Days 1, 8, and 15; and oral or IV dexamethasone 40 mg weekly. Data is administered concurrently on 28 days at a dose of 8 mg/kg IV on Days 1 and 2 of Cycle 1, then 16 mg/kg IV weekly from Cycle 1 Day 8 through completion of Cycle 2. For Cycles 3-6, pts receive Data 16 mg/kg IV every 2 weeks from Cycle 7 onward, pts receive Data 16 mg/kg IV every 4 weeks, whether with CyBorD or alone during the maintenance phase. Pts receive 4 to 8 induction cycles of Data-CyBorD and eligible pts may undergo an autologous stem cell transplant. All eligible pts then receive 12 cycles of maintenance therapy with Data 16 mg/kg IV every 28 days. The primary endpoint is complete response (CR) plus very good partial response (VGPR) on Days 1-4, 8, and 11; and d 40 mg weekly; every 21 days. In the Dara-RVd group only, data 16 mg/kg IV is given on Days 1, 8, 15, and 21 cycles 1-4 and on Day 1 of cycles 5-6. In the Dara-RVd group only, data 16 mg/kg IV is given every 56 days in the Dara-RVd group only. Inclusion criteria include ≥ 18 years of age; documented MM per IWG 2015 criteria; an Eastern Cooperative Oncology Group performance status score of 0, 1, or 2; no or one prior line of therapy. The estimated primary endpoint analysis date is February 2018.

Clinical trial identification: NCT02951819

Legal entity responsible for the study: Janssen Scientific Affairs, LLC

Funding: Janssen Scientific Affairs, LLC


A double blind randomized phase 2 PILOT study of ERYASPASE in patients with acute lymphoblastic leukemia/lymphoma

N. Soule1, C. Holford2, R. Kay2, D. Tilton1, N. Biswas-Baldwin2, I. El Hariry2, M. Sharma1

[Clinical, Erytech Pharma Incorporated, Cambridge, MA, USA, 1Clinical, Erytech Pharma, Lyon, France]

Background: Asparaginase is a critical agent in the treatment of ALL. This enzyme deaminates asparagine, interfering with protein synthesis and resulting in cell death as lymphoblasts are deficient in asparagine synthetase. Eryaspase is a dispersion of homologous red blood cells (RBCs) encapsulating L-asparaginase formulated in a preservative solution for infusion. The formulation of eryaspase has evolved during its development. Two sources of L-asparaginase (drug substance) from Medac GmbH can be used as raw material and encapsulated in the RBCs of the native (Kidrolase®) or recombinant L-asparaginase (Spectril®). This study was designed to investigate the PK comparability of both eryaspase formulations: native or recombinant asparaginase as the starting material, when administered as monotherapy and in combination with chemotherapy during induction and consolidation phases for the treatment of children and young adults presenting with ALL/LBL.

Trial design: This is a multicenter, multinational, double-blind, randomized, parallel group Phase 2 study of patients with de novo or relapsed ALL/LBL. After obtaining informed consent and performance of screening procedures, patients will be randomized to receive either eryaspase-N or eryaspase-R. Major Inclusion: Male or female, aged between 1-35 years. Conformed diagnosis of Philadelphia chromosome negative ALL/LBL, de novo or first relapse. Adequate Performance Status Major Exclusion: Second intention asparaginase treatment in first-line setting. (These are patients who develop hypersensitivity reactions to another asparaginase and require switch to a different asparaginase formulation to complete the intended course of therapy) Refractory ALL/LBL (failure to achieve complete remission in first-line treatment) Recruitment will continue until 38 patients with a PK evaluable profile are enrolled.

Legal entity responsible for the study: Erytech Pharma

Funding: Erytech Pharma


Phase 2 randomized study of daratumumab (dara), lenalidomide (Rd), bortezomib (Vd), and dexamethasone (Rd) in relapsed and refractory MM (pts) with newly diagnosed multiple myeloma (MM) eligible for high-dose therapy (HDT) and autologous stem cell transplantation (ASCT)

T. Lin1, L. Hydutska2, H. Parros1, S. Murphy1, H. Pei1, A. Londhe1, J. Ukropec1, M. Qi6, T. Lutska1, M. Sharma1

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Background: Data is an anti-CD38 antibody approved for the treatment of relapsed and refractory MM. Addition of data to Rd will increase the stringent CR (sCR) rate by the end of post-ASCT consolidation therapy.

Trial design: This is a multicenter, randomized, open-label, active-controlled study in newly diagnosed MM pts eligible for HDT and ASCT achieving high response rates in previously untreated MM. The primary objective of this study is to determine if the addition of data to RVd will increase the stringent CR (sCR) rate by the end of post-ASCT consolidation therapy.

Eligibility: This is a multinational, multinational, double-blind, randomized, parallel group Phase 2 study of patients with de novo or relapsed ALL/LBL. After obtaining informed consent and performance of screening procedures, patients will be randomized to receive either eryaspase-N or eryaspase-R. Major Inclusion: Male or female, aged between 1-35 years. Conformed diagnosis of Philadelphia chromosome negative ALL/LBL, de novo or first relapse. Adequate Performance Status Major Exclusion: Second intention asparaginase treatment in first-line setting. (These are patients who develop hypersensitivity reactions to another asparaginase and require switch to a different asparaginase formulation to complete the intended course of therapy) Refractory ALL/LBL (failure to achieve complete remission in first-line treatment) Recruitment will continue until 38 patients with a PK evaluable profile are enrolled.

Legal entity responsible for the study: Janssen Research & Development, LLC

Funding: Janssen Research & Development, LLC

Method Of Determining The Sensitivity Of Cancer Cells To EGFR Inhibitors

Background: Peripheral T-cell lymphoma (PTCL) refers to a heterogeneous group of tumors that comprise a subset of T-cell non-Hodgkin lymphomas. PTCL-not otherwise specified, angioimmunoblastic T-cell lymphoma, and anaplastic large cell lymphoma are among the most common of these rare tumors. Outcomes are often poor, particularly in the setting of relapsed or refractory disease, making PTCL an ideal candidate for the assessment of a novel agent with strong biologic rationale. ALRN-6924 is a cell-penetrating stapled alpha-helical peptide designed to equitably disrupt the interaction between the p53 tumor suppressor protein and its endogenous inhibitors, murine double minute X (MDMX) and 2 (MDM2). For TP53 wild-type (WT) tumors, pharmacological disruption of this interaction offers a means to induce p53-dependent cell cycle arrest and apoptosis, resulting in antitumor efficacy via a novel mechanism. ALRN-6924 demonstrated intriguing antitumor activity in a first-in-human phase 1 trial across a variety of tumor types (Merin-Bernstein et al., ASCO 2017, abstract #2905).

Trial design: This open-label Phase 2a study (NCT02246413) will enroll up to 20 adults with relapsed or refractory PTCL, after at least one prior systemic anticancer chemotherapy. Enrolled patients must have TP53 WT T-cell lymphoma (as confirmed by a central NGS testing), ECOG status of 0 or 1, and adequate organ function. Patients will receive 3.1 mg/kg ALRN-6924 as a one-hour infusion on days 1, 8, 15, and 28 of 28-day cycles. Treatment will continue until disease progression or unacceptable toxicity. Response will be assessed according to the revised 2014 International Working Group (IWG) criteria for Lymphoma (Lugano Classification), (Cheson et al., J Clin Oncol. 2014;32:3059-3067). Primary objectives are to assess overall response rate and to further evaluate the safety and tolerability of ALRN-6924. Secondary objectives include assessment of time to response, duration of response, progression free survival, and overall survival. Pharmacodynamic biomarkers will be measured in blood and tumor samples. Recruitment is ongoing.

Clinical trial identification: NCT02246413

Legal entity responsible for the study: Aileron Therapeutics, Inc.

Funding: Aileron Therapeutics, Inc.


Funding: Aileron Therapeutics, Inc.

Disclosure: R. Schlenk: Reports grants and personal fees from Novartis, grants from Amgen, grants and personal fees from Pfizer, grants from Astrazeneca, grants from PharmMar. H. Dombret: Grants and personal fees – Pfizer, Incyte, Jazz Pharma, Janssen, Bayer, Aileron, Puma, Verastem, Cytoxon, Incyte, Zymeworks, Ebusstage. D. Weinstock: Research funding: Aileron Therapeutics. M. Aivado, D.A. Amere: Employee of Aileron Therapeutics, with equity. All other authors have declared no conflicts of interest.

Annals of Oncology
MP0250 – a dual inhibitor of VEGF and HGF – plus bortezomib + dexamethasone in a phase 2 open-label, single-arm, multicenter trial in patients with refractory and relapsed multiple myeloma (RRMM)

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**Background:** Despite recent advances in the treatment of multiple myeloma (MM), patients eventually relapse, requiring multiple lines of treatment. Upregulation of both the vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF) pathways has been implicated in loss of response to therapy and linked to poor prognosis through different mechanisms such as stimulation of angiogenesis, bone destruction, and myeloma cell proliferation and migration. MP0250 is a first-in-class, trispecific multi-DARPin® drug candidate neutralizing VEGF and HGF as well as binding to human serum albumin to increase plasma half-life. MP0250 shows activity in multiple preclinical tumor models among them an MM model in which it enhances the effects of bortezomib on e.g. M protein production and bone lysis. MP0250 has shown a favorable safety profile in a Phase 1 clinical trial in advanced solid tumors.

**Trial design:** This trial is recruiting adults ≥18 years of age with RRMM who have received ≥2 lines of therapy (including bortezomib and an immunomodulatory drug [IMiD]), have not shown any response to and have progressed on or within 60 days of the most recent treatment. The primary endpoint is efficacy in terms of overall response rate (ORR). Secondary endpoints include safety and immunogenicity. A total of 40 patients will be enrolled, 12 patients during a lead-in phase (Part 1) to establish a safe dose and an additional 28 patients in Part 2 to make a total of 34 patients at the target dose. Patients will receive study treatments (MP0250 in combination with bortezomib + dexamethasone) until the end of the study, disease progression, unacceptable toxicity, or other criteria for discontinuation, whichever occurs earlier. Cytogenetic analyses, response assessment, exploratory biomarkers, pharmacokinetics and immunogenicity will be determined in either bone marrow and/or blood/urine. The trial is currently recruiting patients.

**Clinical trial identification:** EUDRACT number: 2016-002771-10

**Legal entity responsible for the study:** Molecular Partners AG

**Funding:** Molecular Partners AG

**Disclosure:** M.S. Raab, R. Ria, J. Schlenzka, A. Vacca, H. Goldschmidt: Has been involved in design of the trial and received study funds through the university for performing the trial. T. Krahne: TK has been involved in statistical design of the trial and received consultancy funds. J. Haunschild, F. Herrmann, U. Fiedler, K. Dawson: JH is a full-time employee of Molecular Partners AG. M.T. Stumpp, A. Harstrick: CSO of Molecular Partners AG. K. Tadjalli Mehr: Medical consultant to Molecular Partners AG.
Durvalumab for recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC): Preliminary results from a single-arm, phase 2 study


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Background: R/M HNSCC patients (pts) who have progressed on platinum-based chemotherapy have a poor prognosis and limited therapeutic options. Programmed cell death 1 (PD-1) and its ligand 1 (PD-L1) are frequently up-regulated in several tumor types, including HNSCC. The global, single-arm, Phase 2 HAWK study (NCT02207530) evaluated the anti-PD-1 immunotherapy durvalumab as monotherapy in PD-L1 high pts with R/M HNSCC who have failed platinum-based chemotherapy.

Methods: Immunotherapy-naïve pts aged ≥18 years with confirmed PD-L1 high protein expression (≥25% of tumor cells [TCs]) using the Ventana SP263 assay who had progression or recurrence during/after 1 platinum-based regimen for R/M HNSCC received durvalumab 10 mg/kg IV every 2 weeks up to 12 months or until progression, starting another anticancer therapy, consent withdrawal, or unacceptable toxicity. The primary endpoint was objective response rate (ORR; blinded independent central review, RECIST v1.1); secondary endpoints included progression-free survival (PFS) and overall survival (OS).

Results: As of Sept 26, 2016, 112 pts from 12 countries had received treatment (median age 60 years, 71.4% male, 34.7% human papillomavirus [HPV]+, and 61.6% current/former smokers). Median durations of treatment and follow-up were 3.45 and 5.96 months, respectively. Among evaluable pts (n = 111), ORR was 13.5% (95% CI 7.8–21.3) overall and 26.5% (95% CI 12.9–44.4) and 7.9% (95% CI 2.6–17.6) for HPV+ and HPV- pts, respectively; among responders (n = 15), 12 (81%) had an ongoing response at data cutoff (DCO); 35 pts (31.5%) had stable disease ≥8 weeks. Median PFS was 2.3 months (95% CI 1.9–3.7) and 34 pts (30.4%) were alive at DCO (OS data were immature). The incidence of grade ≥3 treatment-related adverse events (AEs) was 9.8% and no treatment-related AEs led to death. 88 pts (78.6%) discontinued initial study treatment, 60 (54%) due to progressive disease and 10 (8.9%) due to all-cause AEs.

Conclusions: Durvalumab demonstrated promising antitumor activity with an acceptable safety profile in PD-L1 high pts with R/M HNSCC, supporting its potential use, and the opportunity to improve efficacy, in combination therapy.

Clinical trial identification: NCT02207530 (release date: August 1, 2014)

Legal entity responsible for the study: AstraZeneca PLC

Funding: AstraZeneca PLC

Disclosure: D. Zandberg, PI at UMeGGCC for trials by Medimmune, AstraZeneca, Merck, Macrogenics, Bristol-Myers Squib, Gilbikin, A. Algazi. UCSC receive research funding on my behalf from AstraZeneca, Merck, Bristol-Myers Squib, Medimmune, Acerta, OncoSec, Novartis. A. Jimeno: Consultant for AstraZeneca, one presentation at funding on my behalf from AstraZeneca, Merck, AstraZeneca, Celgene, AbbVie, Genentech, Novartis, Bayer, Bristol-Myers Squibb, GlaxoSmithKline; Consulting fees from: Bristol-Myers Squibb, Bayer, Celgene, AbbVie, AstraZeneca, Merck, J. Fayette: Personal fees from Bristol-Myers Squibb and AstraZeneca. J. Guigay: Research grants to my institution from Bristol-Myers Squibb and AstraZeneca. J. Fayette: Research grants from my institution from Merck. R. Mesita: Speakers Bureau: AstraZeneca, Bristol-Myers Squibb, Merck, Nu Pharma. E.E. Vokes: Board Member: NCI, ASCO, AAMC, JCO, ASH, ASCO, ASH, AUA. J. Fayette: Advisory Board: AstraZeneca, Celgene, GlaxoSmithKline, Genentech; Consulting fees from: Medimmune, AstraZeneca, Merck, Celgene, GlaxoSmithKline, Novartis, Bayer, Bristol-Myers Squibb.

Table: 1044Q Clinical Activity per RECIST v1.1 in PD-L1 Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>IC0/a</th>
<th>IC2/a</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR, n (%)</td>
<td>1.4%</td>
<td>6.2%</td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>1.4%</td>
<td>3.4%</td>
</tr>
<tr>
<td>DCR, n (%)</td>
<td>33%</td>
<td>43%</td>
</tr>
<tr>
<td>mDOR, mo (range)</td>
<td>7.4</td>
<td>26.2 (2.8-45.8)</td>
</tr>
<tr>
<td>mDFS, mo (range)</td>
<td>5.7 (0.5-13.5)</td>
<td>2.6 (0.5-48.4)</td>
</tr>
<tr>
<td>mOS, mo (range)</td>
<td>90 (0.5-26.5)</td>
<td>56 (1.5-16.6)</td>
</tr>
<tr>
<td>1-year OS rate</td>
<td>43%</td>
<td>34%</td>
</tr>
<tr>
<td>2-year OS rate</td>
<td>23%</td>
<td>18%</td>
</tr>
<tr>
<td>3-year OS rate</td>
<td>NE</td>
<td>NE</td>
</tr>
</tbody>
</table>

*Indicates a censored value.
*Data by PD-L1 expression on TC will be presented.

**n = 1 for IC0/a, no estimate for mDOR, n = 6 for IC2/a

IC0 = PD-L1 expression on < 1%; IC1 = 1% to < 5%; IC2 = 5% to < 10%; IC3 = ≥ 10%.

PD-L1 subgroups do not reflect the natural prevalence as not enrolled as an all-comer cohort.

DCR, disease control rate: % of pts with CR, PR and SD ≥ 24 wk;
IC, tumor-infiltrating immune cells; mDOR, median duration of response; TC, tumor cells.

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**Clinical trial identification: NCT01375842**

Legal entity responsible for the study: F. Hoffmann-La Roche Ltd.

Funding: F. Hoffmann-La Roche Ltd.

**Disclosure:** F. Braiteh: Speaking and consulting fees received from Genentech. A.S. Balmanoukian: Speaker’s bureau for Merck, Bristol-Myers Squibb, Genentech, and AstraZeneca. F. S. Hodi: Consultant Merck, Bristol-Myers Squibb, Genentech, EMD Serono, Amgen; Research support to institution from: Bristol-Myers Squibb. B. Liu, L. Molinero, X. Shen: Genentech employee and stock. C. O’Hearn: Genentech employee and Roche stock. All other authors have declared no conflicts of interest.

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**1044PD**

**Adjuvant androgen deprivation therapy for high-risk androgen receptor-positive salivary duct carcinoma**

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**Background:** Salivary duct carcinoma (SDC) is a rare and aggressive subtype of salivary gland cancer, with a median disease-free survival (DFS) of less than 3 years. SDC is an androgen-receptor-positive (AR+) in 67-96% of cases. In incurable recurrent AR+ SDC androgen deprivation therapy (ADT) has an overall response rate of 18-50%. In this study, high-risk AR+ SDC pts were treated with adjuvant ADT to study the efficacy.

**Methods:** In this retrospective study, surgical resected pts who received adjuvant ADT for stage 4a/b AR+ SDC at the Radboudumc (Nijmegen, the Netherlands) or Istituto Nazionale dei Tumori (Milan, Italy) were collected. As control group, surgical resected pts diagnosed with stage 4a/b SDC between 1990-2014, who did not receive adjuvant ADT were collected by a search of the Dutch pathology database (PALGA). Pts were analyzed for DFS and overall survival (OS) by using Kaplan-Meier survival curve.

**Results:** 18 AR+ SDC pts (median age 64 years [range 32-80]) were treated with adjuvant ADT (Nijmegen n = 11; Milan n = 7) for a median duration of 10 months (range 2-31 months). All pts had a nuclear AR-staining pattern in > 70% of the cells. They were treated with bicalutamide monotherapy (n = 10), a LHRH analog (n = 1) or a combination of these (n = 7). Treatment was well tolerated. 17/18 pts (94.4%) also received postoperative radiotherapy, of which 4 pts received concurrent chemoradiotherapy (22.2%). The control group consisted of 110 SDC pts (median age 70 years [range 44-100]). 103/110 pts (93.6%) received postoperative radiotherapy, of which 1 pt received concurrent chemoradiotherapy (0.9%). After a median follow-up of 22 months in the ADT-treated SDC pts and 25 months in the control SDC pts, the 3-year DFS was 53.6% and 34.2% (p = 0.137), the 3-year OS was 68.2% and 52.3% (p = 0.198), respectively. The median DFS and OS were not reached in the ADT-treated SDC pts and were 21 months and 46 months in the control SDC pts.
Conclusions: Adjuvant ADT in high-risk AR + SDC pts did not lead to a significant increase in DFS or OS, but the number of treated pts was limited. Due to the rarity of the disease we could not perform a formal phase II study. Translational research to identify pts which may benefit from ADT is warranted.

Legal entity responsible for the study: Carla M.L. van Herpen

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1046PD

Overexpression of the c-MET proto-oncogene in salivary duct carcinoma patients

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Background: Salivary duct carcinoma (SDC) is a rare and aggressive subtype of salivary gland cancer (SGC). Activation of the cellular MET (c-MET) receptor tyrosine kinase has been implicated in cell proliferation, survival, migration, and invasion. The aim of this study was to evaluate the frequency of MET overexpression and its correlation to clinicopathological factors in SDC.

Methods: 136 patients were collected by a retrospective search of the Nationwide Network and Registry of Histio- and Cytopathology (PALGA) in the Netherlands. Formalin-fixed, paraffin-embedded tumor blocks and hematoxylin and eosin stained slides were requested for pathological review. MET expression was evaluated by immunohistochemical staining on primary tumors. These data were correlated to clinicopathological parameters.

Results: c-MET staining was positive in 54 of 136 tumors (39.7%). Of the 54 tumors, 50 had a cytoplasmatic staining pattern and 23 had a membranous staining pattern, so in 19 tumors both cytoplasmatic and membranous staining was observed. No correlations were found between cytoplasmatic or membranous MET and high stage disease (stage 3 and 4 versus stage 1 and 2, p = 0.606 and p = 0.380 respectively), number of positive lymph nodes (p = 0.263 and p = 0.955 respectively), lymph node ratio (p = 0.192 and p = 0.771 respectively), androgen receptor-status (p = 0.838 and p = 0.258 respectively), HER2-status (p = 0.257 and p = 0.595 respectively), time to recurrence (p = 0.559 and p = 0.999 respectively), time to distant metastases (p = 0.398 and p = 0.666 respectively), or overall survival (p = 0.754 and p = 0.516 respectively). Membranous MET staining occurred more frequently in SDC ex pleomorphic adenoma (14 of 52 tumors) than in the ‘de novo’ SDC (9 of 84 tumors) (p = 0.014). In SDC ex pleomorphic adenoma we also found more HER2-positive tumors (p = 0.041).

Conclusions: Cytoplasmatic and membranous MET are overexpressed in SDC and may be a target for MET-targeted therapy. It is not a prognostic factor for overall survival, possibly because frankly invasive SGCs often show less receptor expression then minimally invasive SGCs or pleomorphic adenomas. The higher expression of c-MET and HER2 in SDC ex pleomorphic adenoma needs further investigation.

Legal entity responsible for the study: Carla M.L. van Herpen

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1047PD

Mammary analogue secretory carcinoma (MASC): clinical characteristics in 28 ETV6-NTRK3 fusion gene confirmed patients

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Background: Recently, a new subtype of salivary gland cancer (SGC), mammary analogue secretory carcinoma (MASC), has been defined, which is characterized by the presence of ETV6-NTRK3 fusion gene. Previously, MASC was mixed up with acinic cell carcinoma (AcCC), polymorphous low grade adenocarcinoma and (cyst)adenocarcinoma. We present the clinical features and outcome of MASC patients are not well known. We aimed to describe the clinical presentation and outcome of MASC.

Methods: Firstly, we re-evaluated the pathological diagnosis of salivary gland cancers with a morphological resemblance to MASC, diagnosed in 4 out of the 8 head and neck centres in the Netherlands, for their presence of ETV6-NTRK3 and also included genetically confirmed prospectively diagnosed cases. The ETV6-NTRK3 fusion gene was analyzed using RT-PCR. Secondly, the clinical characteristics were retrieved from the patient files.

Results: Twenty-eight patients with ETV6-NTRK3 fusion gene positive MASC were included (10 prospectively and 18 retrospectively). Of these 18 retrospective patients 13 patients were previously diagnosed as AcCC, the other 5 patients as (low-grade) adenocarcinoma. The median age at diagnosis was 49 years (range 19 – 83 years), 15 patients (34%) were male. The duration of symptoms varied from 6 weeks until 20 years with a median of 14 months. In 18 patients (64%) the tumor was located in the parotid gland; the other patients had tumours of the minor salivary glands (2), submandibular gland (1), oral mucosa/lip (5) or palate (2). All patients had a T1-2 tumour. One patient had lymph node metastases at diagnosis. All patients underwent surgery of which 4 patients needed re-resection and 12 patients (43%) underwent postoperative radiotherapy. One patient had a local recurrence 50 months after primary surgery, but was cured after second resection. None of the patients had regional recurrences or distant metastases. The median follow-up was 49 months and both the 5- and 10-year overall survival rate were 94%.

Conclusions: MASC is a recently acknowledged new entity of SGC characterized by the ETV6-NTRK3 fusion gene. The clinical course seems to be favourable with a very low rate of recurrences and an excellent survival.

Legal entity responsible for the study: Radboudumc

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Annals of Oncology
Relationship between PD-L1 expression and survival in head and neck squamous cell carcinoma (HNSCC) patients (pts)


Background: A retrospective study was conducted using data from patient medical records and exploratory cut-offs of 1%, 5%, 10%, 25% and 50%. OS was calculated as the number of months from initial HNSCC diagnosis until death and estimated using the Kaplan-Meier method. The log-rank test was used to compare survival curves by PD-L1 subgroup. Median OS was similar between PD-L1 high and low/negative pts (68.9 vs. 47.7 months, respectively) in analyses using the TC1% cut-off. This latter relationship remained after adjusting for baseline covariates using Cox PH models. Results: We identified 214 HNSCC pts with data available for date of death/last follow-up and archival tumor samples. Sample ages ranged from 8 to 227.5 years. Pts ≥18 years old diagnosed with HNSCC between 1989 and 2015 were selected. Demographic and tumor characteristics were compared by PD-L1 expression status. PD-L1 testing was performed using the Ventana PD-L1 SP263 assay. PD-L1 expression was assessed using tumor cell (TC) and immune cell (IC) membrane staining and exploratory cut-offs of 1%, 5%, 10%, 25% and 50%. OS was calculated as the number of months from initial HNSCC diagnosis until death and estimated using the Kaplan-Meier method. The log-rank test was used to compare survival curves by PD-L1 status. PD-L1 expression as a prognostic indicator of OS was further examined in Cox proportional hazards (PH) models. Results: We identified 214 HNSCC pts with data available for date of death/last follow-up and PD-L1 status. Mean (SD) tumor sample age was 63.2 (13.4) years and 70% were male. The Table presents baseline characteristics by PD-L1 subgroup. Median OS was similar between PD-L1 high and low/negative pts classified using the TC ≥25%, IC ≥1%, and IC ≥25% cut-offs. However, median OS was 21.2 months longer in PD-L1 high versus low/negative pts (68.9 vs. 47.7 months, respectively; P<0.05) in analyses using the TC ≥1% cut-off. This latter relationship remained after adjusting for baseline covariates using Cox PH models.

Table: 1049PD Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TC PD-L1 expression</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>High (≥25%)</td>
</tr>
<tr>
<td>No. of pts (%)</td>
<td>118 (55.1)</td>
</tr>
<tr>
<td>Mean (SD) age, years</td>
<td>61.1 (12.9)</td>
</tr>
<tr>
<td>HPV positive, %</td>
<td>45.8</td>
</tr>
<tr>
<td>Present smoker, %</td>
<td>31.4</td>
</tr>
<tr>
<td>Stage IV, %</td>
<td>48.3</td>
</tr>
<tr>
<td>African American, %</td>
<td>22.9</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>68.9</td>
</tr>
<tr>
<td>p-value*</td>
<td>Not reached</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IC PD-L1 expression</th>
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<tbody>
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<tr>
<td>No. of pts (%)</td>
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<tr>
<td>Mean (SD) age, years</td>
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<tr>
<td>HPV positive, %</td>
<td>75 (50.0)</td>
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<tr>
<td>Present smoker, %</td>
<td>53 (35.3)</td>
</tr>
<tr>
<td>Stage IV, %</td>
<td>68 (45.3)</td>
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<tr>
<td>African American, %</td>
<td>31 (20.7)</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>79.0</td>
</tr>
<tr>
<td>p-value*</td>
<td>0.07</td>
</tr>
</tbody>
</table>

P<0.05 p-value comparing high vs. low/negative groups.
Results: Between 06/2013 and 02/2017, 495 pts were included in 42 centers. Data available for 463 pts. Median age 79 years (70-95) with 46% over 80. 74% males. 67% of SGEs was performed by oncologists and 33% by nurses. Mean time to complete SGE was 22 minutes. After SGE, 72% pts were classified as unfit. 52% of pts were further assessed by CGA, 48% among SGE fit pts and 53% among SGE unfit pts. Concordance rate of classification Unfit/Fit by SGE and CGA was 81%. Among pts planned to be treated by curative radiotherapy (RT) or chemotherapy (CT) after oncologic evaluation alone, the planned treatment changed after SGE for 8% of pts: addition of CT/biotherapy to RT for 4% or deletion of CT for 4%. Rate of pts requiring multidisciplinary interventions was significantly higher when the assessment was also performed by geriatricians (71 vs 51%), even after adjusting for frailty.

Conclusions: A CGA-based SGE for use by oncologist in older pts with HNSCC seems formed by geriatricians (71% vs 51%), even after adjusting for frailty.

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Conclusions: A CGA-based SGE for use by oncologist in older pts with HNSCC seems formed by geriatricians (71% vs 51%), even after adjusting for frailty.
Results: Between Jun 8, 2015 and Jan 1, 2017, 80 patients were randomly assigned, 41 to the CP+B group and 39 to the CP group. ORR showed a numerical improvement with CP+B group (85.4% vs 69.2%) although with no statistical difference (p = 0.084). The median PFS was 7.23 months in the CP+B group and 7.00 months in the CP group (p = 0.506). OS had not yet matured. Safety was similar in two groups. No bevacizumab related serious adverse events were observed specially including bleeding. Conclusions: CP+B regimen showed a numerical advantage in ORR among NPC patients. Given the limited sample size of our study, further research is needed to evaluate efficacy of bevacizumab in NPC.

Clinical trial identification: NCT02250599 Protocol Registration Receipt: 09/26/2014

Legal entity responsible for the study: the Institutional Review Board and academic committee of Sun Yat-Sen University Cancer Center

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Refining staging system for nasopharyngeal carcinoma treated with intensity-modulated radiation therapy

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Background: We incorporated baseline plasma EBV DNA into refinement of stage groups for nasopharyngeal carcinoma (NPC) treated with radical intensity-modulated radiation therapy (IMRT).

Methods: Patients with non-metastatic NPC treated with radical IMRT +/- adjunct chemotherapy based on 7th edition of American Joint Committee on Cancer (AJCC) system were recruited prospectively from 2010 to 2016. All patients had baseline and serial post-IMRT plasma EBV DNA (in copies/ml) measured and were staged with MRI and PET-CT. Recursive partitioning analysis (RPA) with repeated internal validations derived new stage groups with incorporation of baseline plasma EBV DNA. Multivariable analyses were used to calculate adjusted hazard ratios (AHRs) to derive a new set of AHR stages. Comparison of performance of survival prediction among these 3 sets of stage groups was done to find the best-performing stage set.

Results: The cohort included 520 patients treated with IMRT +/- adjunct chemotherapy with a median follow-up of 5.6 years. They were re-staged on 8th edition of AJCC system. 5-year overall survival (OS) and cancer-specific survival (CSS) were as follows: stage I (OS 89.5%; CSS 100%), II (OS 87.8%; CSS 94.7%), III (OS 85.0%; CSS 90.0%) and IV (OS 74.4%; CSS 79.9%) (p = 0.038 and p = 0.003 respectively). RPA derived NPC into 3 new stages with corresponding OS and CSS: RPA-I (T1-T4N0-N2 & T1-T2N3 & EBV DNA < 2000) (OS 89.1%; CSS 95.2%), RPA-II (T1-T4N0-N2 & T1-T2N3 & EBV DNA > 2000) (OS 80.5%; CSS 84.1%) and RPA-III (T3-T4N3) (OS 58.2%; CSS 67.1%) (both p < 0.001 and p < 0.001 respectively). AHR (I: T1-T2N0-N2; II: T1-T2N0-N2; III: T3-T4N3) after adjusting age, smoking status, treatment (chemoradiation vs. IMRT alone), baseline LDH and plasma EBV DNA also yielded a valid classification (p < 0.001 for both OS and CSS) but was worse on survival prediction compared to RPA. The RPA stages demonstrated better survival prediction especially on CSS after 1000 bootstrapping replicates (bootstrap scores OS: 0.469; CSS: 0.732) than AHR stages (OS: 0.436; CSS: 0.206) and 8th edition AJCC (OS: 0.095; CSS: 0.043).

Conclusions: A novel RPA-based TNM stage groups revealed significantly better survival prediction compared with the 8th edition AJCC and AHR stages.

Clinical trial identification: NCT02476669

Legal entity responsible for the study: Department of Clinical Oncology, The University of Hong Kong and Clinical Oncology Centre, The University of Hong Kong-Shenzhen Hospital

Funding: SK Yee Medical Foundation

Disclosure: All authors have declared no conflicts of interest.

A New Classification for Nasopharyngeal Carcinoma

H.C.S. Cheng 1, C-F. Hong 2

1Radiation Oncology, Koo Foundation Sun Yat-Sen Cancer Center, Taipei, Taiwan, 2Clinical Research, Koo Foundation Sun Yat-Sen Cancer Center, Taipei, Taiwan

Background: This study is to develop and validate a new classification for nasopharyngeal carcinoma (NPC).

Methods: Fifteen hundred and twenty-eight (1528) newly diagnosed NPC patients treated between 1995 and 2010 were included in this study. Seven hundred and one patients (n = 701) were treated with 3D conformal radiotherapy (3D-RT) and 827 patients were treated with IMRT. Cox proportional hazards model was used to select the significant split node to partition patients into the different risk group. Recursive partitioning analysis derived a new classification in patients treated with 3D-RT objectively. This new staging system was then validated in patients treated with IMRT.

Results: The median follow-up interval was 84.6 months (range 2-175 months). According to the 7th AJCC staging system, the stage I patients showed a 5-year overall survival (OS) rate of 93.8%, stage II of 94.5%, stage III of 87.9%, stage IVA of 71.5%, stage IVB of 61.3%, and stage IVC of 5.8% (p < 0.0001). In the validation group (n = 827), the Group I in new system was patients with stages of T1-3N0-1 and T1N2 (n = 364); their 5-year OS was 92.4%. The Group II was patients with stages of T2N2 (n = 175); their 5-year OS was 86.0%. The Group III was patients with stages of any T4 and N3 (n = 249); their 5-year OS was 72.0%. The Group IV was patients with distant metastasis (n = 36); their 5-year OS was 17.9%. This new classification system will be compared to the 8th AJCC staging system.

Conclusions: We propose a new staging system for NPC, which distributes more patients in the early stage.

Table: 1054PD Patient Distribution According to Chinese 2008 and the 7th AJCC staging systems

<table>
<thead>
<tr>
<th>Stage</th>
<th>Chinese 2008 staging</th>
<th>2010 AJCC staging</th>
<th>Current proposal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>2.3%</td>
<td>2.3%</td>
<td>42.9%</td>
</tr>
<tr>
<td>Stage II</td>
<td>11.0%</td>
<td>23.7%</td>
<td>21.9%</td>
</tr>
<tr>
<td>Stage III</td>
<td>39.4%</td>
<td>49.1%</td>
<td>30.0%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>47.3%</td>
<td>24.9%</td>
<td>5.2%</td>
</tr>
</tbody>
</table>

Legal entity responsible for the study: None

Funding: Koo Foundation Sun Yat-Sen Cancer Center

Disclosure: All authors have declared no conflicts of interest.
primary endpoint of OS and additional endpoint of safety by best overall response (complete or partial response [CR/PR], stable disease [SD], or progressive disease [PD]), assessed by investigators per RECIST 1.1 every 6 weeks beginning at week 9.

Results: The minimum follow-up was 11.4 mo. Baseline demographics were similar across response groups and treatment arms. Median duration of therapy for nivolumab-treated pts with CR/PR, SD, and PD was 12.5 mo, 4.2 mo, and 1.6 mo, respectively. Estimates of median OS, 12-mo, and 18-mo survival rates favored nivolumab vs IC in the CR/PR and SD response groups (Table). The incidence of grade 3—4 treatment-related adverse events was lower for nivolumab vs IC, within each of the response groups (CR/PR, SD, and PD).

Conclusions: Pts with CR/PR and SD had improved median OS and survival rates with nivolumab relative to single-agent standard therapy. Nivolumab’s safety profile was favorable vs IC, including for pts with CR/PR whose median duration of therapy was greater than a year.

Clinical trial identification: NCT02105636

Legal entity responsible for the study: Bristol-Myers Squibb

Funding: Bristol-Myers Squibb

Disclosure: L. Licitra: Reports consultant/advisory support from Eisai, Bristol-Myers Squibb, MSD, Merck-Serono, Boehringer-Ingelheim, Novartis, AstraZeneca, Bayer Roche and honoraria/consultation fees from Eisai, Bristol-Myers Squibb, MSD, Merck Serono, Debiopharm, Sobi, AstraZeneca. R.L. Ferris: Reports other from Amgen, other from AstraZeneca/MedImmune, other from Bristol-Myers Squibb; other from EMD Serono, other from Lilly, other from Merck, other from Pfizer, other from VentRx Pharmaceuticals, during the conduct of the study. G. Blumenschein Jr.: Reports grants from Merck, AstraZeneca, Celgene, AbbVie, Genentech, Xeroxer, Novartis, Bayer, Bristol-Myers Squibb, GSK, during the conduct of the study; other from Bristol-Myers Squibb, Bayer, Celgene, Clovis, AbbVie, Ariad, AstraZeneca, Merck, outside the submitted work. K.J. Harrington: Reports honoraria and advisory board roles from AstraZeneca, Bristol-Myers Squibb, Merck, MSD, Pfizer and research grants from MSD J. Guigay: Grants to institution: Bristol-Myers Squibb, Boehringer-Ingelheim, GlaxoSmithKline, Merck Serono. S. Kasper: Reports consultant/advisory support from Biogen Idec, during the conduct of the study; research grants from Novo Nordisk, outside the submitted work; honoraria from ONO PHARMA, Bristol-Myers Squibb, Merck Serono, Eisai and Bayer. M. Monga: Reports other from Bristol-Myers Squibb, during the conduct of the study. M. Lynch: Dr Lynch in an employee of Bristol-Myers Squibb. L. Li: Employee of Bristol-Myers Squibb. M.L. Gillison: Reports personal fees from Celgene, Lilly, Amgen, GlaxoSmithKline; grants and personal fees from Bristol-Myers Squibb, Merck, AstraZeneca, grants from Kyowa, during the conduct of the study. J. Fayette: Reports personal fees from Bristol-Myers Squibb and AstraZeneca, outside the submitted work.

Table: 1055P

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<tr>
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<th>CR/PR</th>
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<th>PD</th>
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<tr>
<td></td>
<td></td>
<td>Nivolumab (n = 32)</td>
<td>IC (n = 7)</td>
<td>Nivolumab (n = 55)</td>
<td>IC (n = 43)</td>
<td>Nivolumab (n = 100)</td>
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<tr>
<td>Median OS, mo(95% CI)</td>
<td></td>
<td>NR</td>
<td>13.6</td>
<td></td>
<td>10.4</td>
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<tr>
<td></td>
<td></td>
<td>(NR, NR)</td>
<td>8.9</td>
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<td>(8.7, 15.2)</td>
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<tr>
<td>HR (95% CI)</td>
<td></td>
<td>0.08 (0.01, 0.47)</td>
<td>57.1</td>
<td></td>
<td>0.53 (0.33, 0.85)</td>
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<tr>
<td>12-mo OS rate, % (95% CI)</td>
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<td>96.8</td>
<td>17.2</td>
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<td>46.1</td>
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<td></td>
<td></td>
<td>(79.2, 99.5)</td>
<td>83.7</td>
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<td>(32.4, 58.7)</td>
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<tr>
<td>18-mo OS rate, % (95% CI)</td>
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<td>86.1</td>
<td>38.1</td>
<td></td>
<td>32.6</td>
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<td></td>
<td></td>
<td>(67.0, 94.6)</td>
<td>71.6</td>
<td></td>
<td>(20.0, 45.8)</td>
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NR = not reached

Table: 1056P

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n = 236)</th>
<th>IC (combined) (n = 111)</th>
<th>Cetuximab (n = 13)</th>
<th>Docetaxel (n = 52)</th>
<th>Methotrexate (n = 46)</th>
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<tbody>
<tr>
<td>Number of grade 3—4 TRAEs requiring treatment (%)</td>
<td>28/88 (31.8)</td>
<td>60/88 (68.2)</td>
<td>2/60 (3.3)</td>
<td>36/60 (60.0)</td>
<td>22/60 (36.7)</td>
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<tr>
<td>Total estimated cost of managing grade 3—4 TRAEs, $</td>
<td>253,067</td>
<td>545,374</td>
<td>17,855</td>
<td>333,307</td>
<td>194,211</td>
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<tr>
<td>Cost of managing grade 3—4 TRAEs, mean per treated patient, $</td>
<td>1072</td>
<td>4913</td>
<td>1373</td>
<td>6410</td>
<td>4222</td>
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</table>
Conclusions: Patients with platinum-refractory R/M SCCHN treated with nivolumab had fewer grade 3–4 TRAEs, lower estimated total costs of managing TRAEs, and reduced TRAE costs per treated patient compared with standard, single-agent systemic therapy.

Clinical trial identification: NCT01935921

Legal entity responsible for the study: Catalan Institute of Oncology

Funding: None

Disclosure: All authors have declared no conflicts of interest.

---

**Table 1058P**

<table>
<thead>
<tr>
<th>Table: 1058P</th>
<th>All cohort n = 46 n (%)</th>
<th>Progression n = 36</th>
<th>No EP n = 27</th>
<th>EP n = 9</th>
<th>p value</th>
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<tr>
<td>Age</td>
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<td></td>
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<td></td>
</tr>
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<td>58</td>
<td>56</td>
<td>58</td>
<td>0.6</td>
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</tr>
<tr>
<td>Smokers</td>
<td>39 (85)</td>
<td>22</td>
<td>8</td>
<td></td>
<td></td>
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<tr>
<td>PDL-1 n = 33 Positive Negative</td>
<td>42 (91)</td>
<td>24</td>
<td>9</td>
<td>0.6</td>
<td></td>
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<tr>
<td>Locoregional disease (LRD) Metastatic without LRD</td>
<td>21 (45) 22 (48)</td>
<td>14 11</td>
<td>2.6</td>
<td>0.2</td>
<td></td>
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<tr>
<td>Previsos systemic therapy 0 1 2 ≥3</td>
<td>33 (71) 13 (29)</td>
<td>22 5</td>
<td>5.4</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>OR (n = 44)</td>
<td>3 (7) 11 (24) 30 (65) 2 (4)</td>
<td>1 5 20 1</td>
<td>0 2 6 1</td>
<td>0.5 0 7 0.4</td>
<td></td>
</tr>
<tr>
<td>TGR increase</td>
<td>13 (28)</td>
<td>9</td>
<td>2</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>C5 (n = 50)</td>
<td>23 (58)</td>
<td>17</td>
<td>4</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>AntitPDL-1 AntiPDL-1 + CTLA-4 Immunomodulator (IMD)</td>
<td>9 (20) 11 (24) 16 (35) 4 (9) 2 (3) 4 (9)</td>
<td>5 8 7 4 1 2</td>
<td>2 1 5 0 1 0</td>
<td>0.6 0 5 0 1 0 5 0.4 1</td>
<td></td>
</tr>
<tr>
<td>Tumor complications</td>
<td>8 (17)</td>
<td>3</td>
<td>5</td>
<td>0.013</td>
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</tbody>
</table>
Conclusion: PD-L1 IHC 28-8 pharmDx has shown to be reproducible and robust in detecting PD-L1 expression in FFPE human SCCHN specimens using the Autostainer Link 48.

Legal entity responsible for the study: Agilent Technologies, Inc.

Funding: Agilent Technologies, Inc. and Bristol-Myers Squibb


Programmed death ligand-1 overexpression is a poor prognostic factor for Human papillomavirus-positive tonsillar squamous cell carcinoma

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Background: Programmed death ligand-1 (PD-L1) plays a key role for immune evasion, contributing to carcinogenesis and tumor progression. Tonsillar squamous cell carcinoma (TSCC) is the most common human papillomavirus (HPV)-associated oropharyngeal cancers and they frequently present with locally advanced diseases and cervical metastases, which are associated with poor prognoses. Recent studies have reported the close association between PD-L1 and HPV in head and neck SCCs. However, its clinical and prognostic significances in TSCCs remain controversial.

Methods: Immunohistochemical analysis of PD-L1 was performed in 79 formalin-fixed paraffin-embedded blocks of surgically resected specimens. Peptide nucleic acid-based HPV chip test was used for detection of HPV.

Results: PD-L1 expression was observed in 19 cases (24.1%), and clinicopathological features such as invasion to base of tongue, lymphatic invasion, infiltrative tumor border, younger age (<60 years), left side location, and lymph node metastasis represent significant risk factors associated with PD-L1 overexpression in TSCCs. HPV tended to be associated with PD-L1 overexpression, which showed borderline statistical significance (P = 0.066). PD-L1 expression was a strong indicator for poor overall survival but not for disease-free survival. Notably, PD-L1 overexpression had significant effects on worse overall and disease-free survivals in HPV-positive TSCCs. Multivariate analysis revealed that PD-L1 overexpression was an independent prognostic factor for overall survival (P = 0.049, hazard ratio 2.796).

Conclusions: PD-L1 overexpression may predict a poor prognosis and a high risk of recurrence in TSCC patients, especially in HPV-positive tonsillar cancers, implying PD-L1 could be pivotal candidates for a new prognostic and predictive biomarker in tonsillar cancer.

Legal entity responsible for the study: none

Funding: None

Disclosure: All authors have declared no conflicts of interest.
(n = 27), neoadjuvant IRX-2 significantly increased lymphocyte infiltration (LI) into resected head and neck tumors. Increased LI was associated with changes in fibrosis and necrosis in resected tumors, 65% event-free survival (EFS) at 2 years, and 69% overall survival (OS) at 5 years, better than rates for historical matched controls. Patients with LI greater than the median had improved OS compared to those below the median. This sub-study was undertaken to define the mechanisms responsible for the increase in LI with neoadjuvant IRX-2.

Methods: Matched pre- and post-treatment tumor specimens from 7 phase 2a study patients were interrogated with two immune-profiling technologies, multiplex immunohistochemistry (IHC, PerkinElmer, Waltham, MA) and transcriptome analysis (Nuscale Technologies, Seattle, WA).

Results: Multiplex IHC provided detailed visualization and quantitation of various immune cells in the tumor microenvironment (TME), supporting previous phase 2a pathology findings. Transcriptome analysis provided a global snapshot of the TME, quantitative information on immune cell subsets, and insights into possible mechanisms for changes in LI. Consistent with IRX-2 activation of multiple immune cells in the TME, mRNA expression of B-cell, CD4+ T cell, CD8+ T cell, and dendritic cell functional genes was increased on average by 1.73, 1.06, 1.39, and 1.36, respectively, following treatment with IRX-2. Increases in chemokine gene expression were observed, suggesting that IRX-2-induced production of chemokines may in part drive tumor LI. Strong evidence of functional immune activation uncovered by transcriptome analysis included an increase in interferon γ pathway gene expression and induction of regulatory checkpoint pathways.

Conclusions: Neoadjuvant IRX-2 promotes tumor LI and prolongs EFS and OS in patients with head and neck squamous cell carcinoma. Immune profile analyses provided insights into the pathways potentially responsible for IRX-2-induced increases in LI and overall immune activation.

Legal entity responsible for the study: IRX Therapeutics, Inc.

Funding: IRX Therapeutics, Inc.


Phenotyping of the immune infiltrate in oropharyngeal squamous cell carcinoma: Focus on materials and methods

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Background: Stromal CD8+ lymphocytic infiltration constitutes an independent prognostic marker for better overall survival in patients with oropharyngeal squamous cell carcinoma (OSCC). However, scoring of (novel) biomarkers is often compromised by the lack of standardised methodology which hampers their use in daily clinical practice. We therefore performed a comparative analysis to evaluate the importance of choice of materials and methods in CD8 assessment in patients with OSCC. Other immune cell markers, that is, CD3 and FoxP3 were taken into account as well.

Methods: Immunohistochemical analysis of CD3, CD8 and FoxP3 was performed on whole-tissue sections from 101 treatment-naive patients with OSCC. A comparison of biopsy material versus resection material for expression of the CD3+ T cells (p = 0.712, p = 0.853), CD8+ T cells (p = 0.659, p = 0.764) and FoxP3+ T cells (p = 0.783, p = 0.802) was performed.

Table: 1064P OS of HDC vs LDC

<table>
<thead>
<tr>
<th>Group</th>
<th>Unadjusted HR for OS</th>
<th>95% CI</th>
<th>PS Adjusted HR for OS</th>
<th>95% CI</th>
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| 1063P Phenotyping of the immune infiltrate in oropharyngeal squamous cell carcinoma: Focus on materials and methods

A. de Meulenaere1, T. Vermassen1, S. Rottey1, L. Ferdinande2

1Department of Medical Oncology, Ghent University Hospital, Ghent, Belgium; 2Department of Medical and Forensic Pathology, Ghent University Hospital, Ghent, Belgium

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<th>PS Adjusted HR for OS</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n = 2,820)</td>
<td>0.85</td>
<td>0.77-0.94</td>
<td>0.89</td>
<td>0.80-1.01</td>
</tr>
<tr>
<td>Oral Cavity (n = 182)</td>
<td>0.77</td>
<td>0.56-1.1</td>
<td>0.72</td>
<td>0.50-1.10</td>
</tr>
<tr>
<td>Hypopharynx/Larynx (n = 1,026)</td>
<td>1.00</td>
<td>0.86-1.20</td>
<td>1.1</td>
<td>0.90-1.30</td>
</tr>
<tr>
<td>Oropharynx (n = 1,590)</td>
<td>0.78</td>
<td>0.70-0.90</td>
<td>0.81</td>
<td>0.69-0.96</td>
</tr>
</tbody>
</table>
3-weekly or weekly cisplatin concurrently with radiotherapy for patients with locally advanced squamous cell carcinoma of the head and neck: A multicentre, retrospective analysis


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Background: Concurrent chemoradiotherapy with cisplatin is standard for patients (pts) with loco-regionally advanced squamous cell carcinoma of the head and neck (LA-SCCHN). The standard regimen includes 3-weekly cisplatin, but weekly regimens are often used to lower toxicity. Reaching a cumulative dose of >200 mg/m² cisplatin is shown being associated with improved outcome. We herein investigated cumulative dose reached and toxicity between the both widely used 3-weekly and weekly cisplatin regimens with concurrent radiotherapy.

Methods: Multicentre, retrospective analysis of all patients with LA-SCCHN treated at 3 centres in Switzerland between 06/2008 and 12/2015. We used descriptive statistics and logistic regression (uni- and multivariable) to investigate the association between the chosen cisplatin regimen (weekly versus 3-weekly) and the chance to reach the cumulative cisplatin dose of >200 mg/m². Landmark approach (8 weeks after start of treatment) was applied for investigating the prognostic impact of the cumulative cisplatin dose on survival using Cox regression techniques.

Results: We included 174 pts (3-weekly schedule, N = 127; weekly schedule, N = 187). Median cumulative cisplatin dose was 200 mg/m² (Q25-75 = 150-300) for pts treated with a 3-weekly schedule and 160 mg/m² (120-240) for the weekly schedule, consequently more pts treated with a 3-weekly schedule reached a cumulative dose >200 mg/m² (75.6% vs 47.3%, p < 0.001). This association was also observed in multivariable analysis adjusted for age and sex (OR 3.46, 95% confidence interval [CI], 2.1 - 5.7). The 3-weekly regimen vs. 47.1%, p < 0.05). Conclusions: Significantly more patients receive a cumulative dose of >200 mg/m², when treated with a 3-weekly schedule compared to weekly dosing. This comes at the cost of more renal toxicity. Due to the non-randomized nature of this analysis, no conclusions on the efficacy of the respective schedules should be drawn.

Legal entity responsible for the study: University Hospital Basel

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Hyperfractionated twice daily re-irradiation (bid re-RT) and chemotherapy (CT) for locoregionally recurrent head and neck squamous cell carcinoma (LR HNSCC): A systematic review (SR)

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Background: Re-RT +/- CT is a salvage option for patients (pts) with LR HNSCC in a previously irradiated field, although efficacy and toxicity, and the optimal treatment regimen remains undefined due to a lack of randomized trials. Hyperfractionated bid re-RT, by reducing the dose per fraction may improve radiation (RT) therapeutic ratio and is increasingly used in LR HNSCC. The aim of this SR is to assess the treatment outcome of bid re-RT in LR HNSCC.

Methods: We conducted a SR of MEDLINE, EMBASE and the Cochrane library up to Nov 2016 for clinical trials of bid re-RT + CT in pts with LR HNSCC. Paired reviewers selected studies for inclusion and extracted data. Individual patient overall survival (OS) data were extracted where possible from published Kaplan-Meier (KM) curves to construct an aggregate KM curve.

Results: We identified 18 clinical trials (all were phase 1 or 2) with 404 pts. Median (of reported medians) prior RT dose was 64Gy, and median time from prior RT was 30.9m. Seventy-three and 156 pts respectively had CT and surgery as part of 1st line treatment. Median re-RT dose was 60Gy administered as continuous or split courses. The re-RT fields consisted of gross tumor volume plus a margin of 1-2 cm. All CT regimens were combinations either with cisplatin (n = 6) or 5-FU (n = 4), given concurrently with (n = 9) or prior to (n = 1) re-RT. Twenty-eight (7%) pts had delaying surgery prior to re-RT. In pts who were analyzable for toxicities, acute events (>1/grade 3) were reported in 252 of 377 (67%) pts and late events (>90d post re-RT) in 87 of 333 (26%) pts. Treatment-related deaths occurred in 26 (6%) pts, mostly due to infection or vascular events. Of the 5 trials with extractable KM curves, estimated median OS was 10.2m (95% CI 8.7-12.6m). 1- and 3-y OS rates were 46.8% and 11.2% respectively. No differences were observed in median OS and toxicity rates based on CT type (Wilcoxon test).

Conclusions: This is the 1st aggregate analysis of bid re-RT and CT in LR HNSCC. Long-term OS was observed in a subset of pts, however treatment-related morbidity was apparent. The optimal re-RT and CT regimen is still undefined and further study is required. Legal entity responsible for the study: None

Funding: None

Disclosure: All authors have declared no conflicts of interest.

The observational ENCORE study: Cetuximab + platinum-based therapy (PBT) for first-line (1L) treatment of patients with recurrent/metastatic squamous cell carcinoma of the head and neck (R/M SCCHN)

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Background: The randomized, phase 3 EXTREME study established cetuximab (CT) in pts with LR HNSCC. However, there is a need for evidence on the efficacy and toxicity of platinum-based CT in pts with R/M SCCHN. This is a phase 3 study comparing the efficacy and toxicity of cetuximab (C), carboplatin (CP) with or without gemcitabine (G).

Methods: Eligible patients (pts) with R/M SCCHN were randomly assigned in a 1:1:1 ratio to receive CT+RP with either RP or FP. The RP group consisted of 2.5mg/m² intravenous raltitrexed on day 1 and 25mg/m² intravenous cisplatin on days 1-3. The FP group consisted of continuous intravenous infusions of 600mg/m² 5-fluorouracil on days 1-3 and 25mg/m² intravenous cisplatin on days 1-3. Chemotherapy was administered concurrently with radiotherapy and was repeated every 3 weeks with completion of at least 2 cycles. Primary endpoint was PFS. Secondary endpoints were complete response rates (CRR), OS and safety.

Results: A total of 108 patients with LA-HNSCC, enrolled in this study, with 52 patients assigned to the RP group and 56 patients to the FP group. The incidence rate of treatment-related adverse events (TRAEs) was similar (P=0.05). Conclusions: The efficacy of the RP regimen was similar to that of the FP regimen. The RP regimen had a tolerable safety profile, with a lower incidence of severe OM and, consequently, an improved quality of life. In conclusion, RP is an effective, well-tolerated regimen for LA-HNSCC.

Clinical trial identification: NCT02485548 Release date: June 26, 2015

Legal entity responsible for the study: Xia He

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Primary surgery versus chemoradiotherapy for advanced oropharyngeal and hypopharyngeal cancer: A propensity-score matched study using a nationwide database

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Medical Research, Koo Foundation Sun Yat Sen Cancer Center, Taipei, Taiwan

Background: Traditionally, advanced head and neck cancer has been managed through surgery with or without postoperative radiotherapy. Studies since the 1980s have been advocating organ preservation therapies using various combinations of chemotherapy and radiotherapy. For treatment of advanced oropharyngeal and hypopharyngeal cancer, there has been a controversy in choosing between primary surgery and chemoradiotherapy. We aimed at conducting a propensity-score matched study from a national database to investigate the survival after primary surgery with or without postoperative radiotherapy versus chemoradiotherapy in patients with advanced oropharyngeal and hypopharyngeal cancer.

Methods: We identified patients with stage III & IVa oropharyngeal and hypopharyngeal cancer between 2004 and 2009 from Taiwan National Health Insurance Claims Database. The study cohort was followed until 2012. We matched patients who received primary surgery to those who received chemoradiotherapy by propensity score calculated by logistic regression. Age at diagnosis, Charlson comorbidity index score, year of cancer diagnosis, clinical stage, receiving chemoradiotherapy, and receiving radiation therapy were well matched in these two groups. Overall survival and disease-free survival were compared using the Kaplan – Meier method.

Results: We identified 1,603 oropharyngeal and 1,512 hypopharyngeal cancer patients. After propensity score matching, 614 patients with oropharyngeal cancer and 638 patients with hypopharyngeal cancer were included in the analysis. For advanced hypopharyngeal cancer (stage III and IVa), the overall survival and disease-free survival in patients receiving primary surgery with or without radiotherapy were statistically better than the matched sample who received chemoradiotherapy. For oropharyngeal cancer, the survival benefit only existed in stage IVa patients who received primary surgery with or without radiotherapy.

Conclusions: The study showed that primary surgery with or without radiotherapy might have survival benefit in patients advanced oropharyngeal or hypopharyngeal cancer as compared to chemoradiotherapy.

Legal entity responsible for the study: Koo Foundation Sun-yat Sen Cancer Center
Funding: Health and Welfare SurchARGE of Tobacco Products grant of Taiwan Cancer Society.

Disclosure: The author has declared no conflicts of interest.
onset of radiotherapy were significant predictors of poorer OS and extracapsular extension, positive margin and longer time between surgery and onset of radiotherapy were significant predictors of poorer DFS.

Conclusions: In our serie, postoperative radiochemotherapy based in weekly cisplatin at 60mg/m² in patients diagnosis of locally advanced squamous cell carcinoma of head and neck offers a good toxicity profile and results comparable to those published in the literature with a 3-weekly cisplatin scheme. The number of positive nodes, longer time between surgery and onset of radiotherapy, extracapsular extension and positive margin were unfavorable prognostic factors related with SLE and OS in the multivariate analysis.

Legal entity responsible for the study: Hospital Ramon y Cajal

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1072P

Effectiveness and toxicities of cetuximab in combination with concurrent chemoradiotherapy in locoregionally advanced nasopharyngeal carcinoma: A propensity score-matched analysis

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Background: There is increasing evidence showing that concurrent chemoradiotherapy (CCRT) may be inadequate for patients with locoregionally advanced nasopharyngeal carcinoma. Until now, no randomized controlled clinical trial has proved the effectiveness of cetuximab plus CCRT.

Methods: There were 681 consecutive stage III-IVB NPC were included in this retrospective study. 75 underwent CCRT with cetuximab and 606 received CCRT. The nasopharyngeal and neck tumor of all patients were treated by intensity modulation radiation therapy (IMRT).

Results: After matching at a 1:2 ratio, 150 patients were treated with CCRT and 75 with CCRT plus C were selected. The 3-year PFS rates (83.7% vs 72.0%, P = 0.030) and 3-year LRFS rates (98.6% vs 90.2%, P = 0.034) were higher for patients in the CCRT plus C arm than with CCRT alone. Furthermore, a marginal trend of increasing risk of 3-year DMFS rates (83.9% vs 78.4%, P = 0.301) and 3-year OS rates (91.2% vs 85.8%, P = 0.123) was found. The results indicated that CCRT plus C treatment was a significant and independent protective predictor for 3-year PFS (P = 0.015) and DMFS rates (P = 0.047). When focusing on stage T4 and/or N3 in the subgroup, the CCRT plus C arm achieved significantly prolonged 3-year PFS (79.9% vs 62.6%, P = 0.022) and a marginally increased OS (88.0% vs 77.9%, P = 0.086) compared with that of CCRT alone. Additionally, the 3-year LRFS (97.0% vs 90.9%, P = 0.216) and DMFS (79.9% vs 67.8%, P = 0.161) were enhanced in patients with CCRT plus C compared to CCRT alone. When concentrating on stage III patients, there were no considerable statistically significant differences found in 3-year PFS, OS, LRFS, and DMFS rates between patients with and without cetuximab. No significant difference was observed in the late toxicities between the two treatments.

Conclusions: This propensity-score matched study reveals that patients with T4 and/or N3 stage could benefit from the combination of cetuximab with the current chemoradiotherapy in locoregionally advanced NPC, although with more acute moderate to severe toxicities. However, this strategy remains to be validated in a prospective randomized controlled study.

Clinical trial identification: This retrospective study has no clinical trial identification.

Legal entity responsible for the study: Department of Radiation Oncology Nanjing Medical University Affiliated Cancer Hospital, Jiangsu Cancer Hospital, Jiangsu Institute of Cancer Research

Funding: The National Natural Science Foundation of China (No. 81672998); Jiangsu Clinical Medicine Science and Technology Special Fund (BL2014091); Jiangsu Provincial Commission of Health and Family Planning Youth Research Project (Q201601)

Disclosure: All authors have declared no conflicts of interest.

1073P

Safety and efficacy of nimotuzumab with concurrent chemoradiotherapy in unselectively locally advanced squamous cell carcinoma of head and neck: Indian rural hospital experience

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Background: The aim of this study was to evaluate the safety and efficacy of nimotuzumab, a humanized monoclonal antibody against epidermal growth factor receptor, in combination with chemoradiation for head and neck squamous cell cancer (HNC).

Methods: The hospital data of 42 patients with HNC who were treated with nimotuzumab from January 2012 to December 2016 were evaluated. Three patients who had undergone prior surgery were excluded and 39 patients diagnosed with locally advanced (stage III-IVb) unresectable HNC who were treated with concurrent chemoradiotherapy with weekly nimotuzumab were considered for final analysis. Tumour response was calculated as per RECIST criteria 1.1. Subgroup analysis was performed to assess association of tumour response with independent variables such as age, gender, histopathological grades and TNM stages using chi square or Fischer exact test. Overall survival (OS) and progression free survival (PFS) was calculated from date of diagnosis using Kaplan-Meier method. All patients were assessed for toxicity and adverse events (AE) were reported as per common terminology criteria for AE v4.0. Statistical analysis was done using SPSS software (v19.0).

Results: At 24 weeks after completion of treatment, objective response rate (complete response [CR] + partial response [PR]) was 97.44% with 26 (66.67%) patients showing CR, 12 (30.77%) patients with PR and one patient (2.56%) had stable disease. Subgroup analysis did not show significant association of tumour response with age, men patients older than 65 years, laryngeal cancer, tumour grade III, TNM stage III showed more complete responses. OS at one year and two years was 100% and 72.9%, while PFS at one year and two years was 87% and 54.40%, respectively. Incidence of grade I, II, III and IV toxicity was 30%, 18.18%, 41.82%, 10%, respectively. No grade V toxicity was observed. Common AE observed were neutropenia (20.91%), mucositis (33.64%), vomiting (18.18%), diarrhoea (2.73%), skin reaction (24.55%). Nimotuzumab was observed to be safe with no additional adverse events (hypersensitivity, allergic reaction and skin changes) were reported during the study period.

Conclusions: Nimotuzumab is an efficacious and safe option when added to concurrent chemoradiotherapy in patients with locally advanced Head and Neck cancer.

Clinical trial identification: 125/12

Legal entity responsible for the study: Dr. Shyamji Rawat

Funding: None

Disclosure: D. Pawar: Works in a Pharmaceutical company. S. Chaudhari: works for Pharmaceutical company. All other authors have declared no conflicts of interest.

1074P

A phase II study of combination chemotherapy with cetuximab/S-1/ low dose cisplatin as neoadjuvant manner for oral squamous cell carcinoma patients

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1Oral & Maxillofacial Surgery 2, Osaka University Graduate School of Dentistry, Suita, Japan, 2Oral & Maxillofacial Surgery, Menova Hospital, Nishinomiya, Japan, 3Oral & Maxillofacial Surgery, Itami City Hospital, Itami, Japan, 4Oral & Maxillofacial Surgery, Ikeda Municipal Hospital, Ikeda, Japan, 5Oral & Maxillofacial Surgery, Rinku General Medical Center, Izumisano, Japan, 6Oral & Maxillofacial Surgery, Higashinosaka City Medical Center, Higashinosaka, Japan

Background: In oral cancer therapy, functional preservation, as well as survival, is a very important matter to consider. One of the methods for organ preservation is an effective preoperative (neoadjuvant) chemotherapy. We previously reported the good antitumor effect and good tolerance of low dose cisplatin/S-1 at ESMO 2004 and 2006. Cetuximab enhances the antitumor effect of cisplatin/S-1 fluorouracil. We investigated the feasibility of combining cetuximab/low dose cisplatin/S-1 chemotherapy as a neoadjuvant regimen for patients with oral squamous cell carcinoma.

Methods: Consecutive patients (n = 14) with newly diagnosed stage II-IV oral squamous cell carcinoma were enrolled in this study from July 2014 to June 2016. Patients were administered 5-10mg/m²/day (day 1-14), cisplatin 5mg/m²/day (day 1-5,6-12) and cetuximab 400mg/m²/day on day 1 and 250mg/m²/day on day 8. This was followed by definitive surgery. Clinical response was assessed by clinical findings and/or CT according to RECIST and histopathological effects were evaluated with surgical specimens.

Results: The rate of clinical response, including complete response (CR) and partial response (PR), was 85.7%. CR 21.8%, PR 64.3%, SD (stable disease) 14.3%. The rate of histological response was 71.4% CR 21.4%, PR 59.0%, no change 26.8%. Toxicities above grade 3 were neutropenia (7.1%), hypokalaemia (7.1%), leukocytopenia (7.1%), thrombocytopenia (7.1%), anorexia (21.4%), diarrhoea (7.1%) and nausea (7.1%). Most toxicities disappeared within 8 weeks after chemotherapy. No serious adverse effects were observed in the majority of patients. Conservative surgery was applied to 12 patients, except 2 patients with SD and 5 of 9 patients who needed reconstruction were able to avoid reconstructive surgery.

Conclusions: Combination chemotherapy with cetuximab/low dose cisplatin/S-1 represents an effective antitumor therapy with mild to moderate toxicities. It is suggested that this regimen is superior to low dose cisplatin/S-1 and can promote function preserving surgery.

Clinical trial identification: UMIN000014632

Legal entity responsible for the study: Individual person

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Background: The standard of care for oral squamous cell carcinoma (OSCC) at present, consists of surgical resection followed by adjuvant radiotherapy and chemotherapy as indicated. However, indications of induction chemotherapy (IC) in OSCC are not clearly defined. This retrospective analysis aimed to investigate the efficacy, toxicity and impact of induction chemotherapy in locally advanced T4b oral cavity squamous cell carcinomas.

Methods: Patients diagnosed with locally advanced T4b OSCC from January 2013 and March 2017 at our centre, who received 2-3 cycles of IC and then assessed for resectability, were reviewed retrospectively. Patients’ profile, response and toxicity of IC, resectability status and overall survival (OS) were evaluated. Statistical analyses were done by SPSS version 17.

Results: Total 134 patients received IC, and out of them 98 (73.1%) were males. Median age at diagnosis was 44 years (range 31-60 years). 107 (79.8%) of our patients received induction chemotherapy (with paclitaxel + cisplatin + 5-FU). Majority of the patients had buccal mucosa cancers (n = 92), followed by gingivo-buccal sulcus (n = 26) and oral tongue (n = 16) primaries. After IC, partial response was achieved in 25 (18.7%) patients, stable disease in 83 (61.9%) patients and disease progression was noted in 26 (19.4%) patients. Post-induction chemotherapy, resectability was achieved in 28 (21%) of 134 patients, but 8 of them did not undergo surgery due to logistic and personal reasons. The median OS of patients with induction regimen (n = 20) was 18.7 months (95% CI: 16.2-21.5 months) and for those treated with non-surgical local therapy (n = 114) was 7.9 months (95% CI: 6.2-9.2 months) (log-rank p = 0.00).

Conclusions: IC may improve the resectability in our patients with T4b OSCC with a manageable toxicity profile. Patients underwent resection had a significantly better median OS than those who received non-surgical local treatment.

Legal entity responsible for the study: Kidwai cancer institute

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1076P Concurrent chemoradiotherapy (CCRT) versus induction docetaxel, cisplatin and 5-fluorouracil (TPP) followed by CORT in locally advanced hypopharyngeal and base of tongue cancer: A randomized phase II study

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Background: To date, clinical trials have not consistently supported the use of induction chemotherapy (IC) for locally advanced head and neck squamous cell cancer (LASCC). Hypopharynx and base of tongue (BOT) cancer has shown relatively poor survival compared to other LASCC. We tried to investigate the role of IC for improvement over current chemoradiotherapy (CRT) in patients with locally advanced hypopharynx and BOT cancer.

Methods: Treatment-naive patients with nonmetastatic stage III/IV hypopharyngeal or BOT cancer were randomly assigned to receive CRT alone (CRT arm: cisplatin 100mg/m² 3 weekly for 2 cycles plus radiotherapy with 64 Gy/34fraction on weekly basis) versus two 21-day cycles of IC (docetaxel 75mg/m² on day 1, cisplatin 75mg/m² on day 1, and fluorouracil 750mg/m² on days 1 to 4) followed by same CRT regimen (IC arm). The primary endpoint was progression-free survival (PFS) and 90 patients are requested to show the superiority of IC arm with one-sided alpha 0.1 and power of 0.85.

Results: This study closed early after enrollment of 36 patients (19 in CRT arm and 17 in IC arm) because of slow accrual. After a median follow up of 47.2 months, there was no significant difference in PFS: the median PFS were 28.6 months for CRT arm and not reached for IC arm (Hazard ratio: 0.65; 95% CI: 0.19-1.60). However, the survival curves widely separated with a plateau after 3 years, suggesting the survival benefit from induction chemotherapy: 3-year PFS rates were 45% and 68%, and 3-year overall survival rates were 62% and 85% (HR: 0.35, 95% CI: 0.07-1.69), in CRT and IC arms, respectively. In both subgroups with BOT and hypopharyngeal cancer, survival outcomes of IC arm were also insignificantly superior to those of CRT arm. All adverse events were manageable and there was no grade 3/4 toxicity except one patient had grade 3 stomatitis in IC arm.

Conclusions: This study failed to demonstrate that induction TPP chemotherapy improves survival in patients with BOT and hypopharyngeal cancer, possibly due to small number of subjects. However, it suggested favorable outcomes with induction chemotherapy, and further large randomized studies are needed to this population.

Clinical trial identification: NCT01132350

Legal entity responsible for the study: Samsung medical center

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1077P Do patients over 70 years with advanced head and neck squamous cell carcinoma tolerate curative intent concurrent chemotherapy-radiotherapy? Predictors of oncological outcomes

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Background: Survival benefit of adding chemotherapy to radiotherapy (RT) in patients (pts) ≥70 yrs of head and neck squamous cell carcinoma (HNSCC) has not been found in literature. Our institutional policy is to offer concurrent chemoradiation (CCRT) to pts > 70 years with a good ECOG status.

Methods: Retrospective analysis of stage III/IV HNSCC in pts ≥70 yrs who received linaclinal based radical CRT with dose equivalent to 70Gy in conventional fractionation (n = 57), between 2006 to 2014 were included.

Results: Pts with stage III/IV (25%/75.4%) HNSCC (n = 57) of oropharynx (n = 15), larynx (n = 18) or hypopharynx (n = 24) underwent radical CRT having mean age 75.18 yrs (range 70-86 yrs) and male to female ratio of 10:41. Pts on CCRT who got cisplatin (CIS) (n = 35) and carboplatin (CARBO) (n = 22) had mean weight loss of 3.53 (range 0-10) kgs. 61.4% completed chemotherapy (defined as cumulative dose of 200mg/m2 of CIS and 5 weekly dose of CARBO @ AUG 2) and 98.2% completed RT without any treatment related death. Higher grades of neutropenia (33.3%) and hypotension (17.5%) with CIS and hypercreatinemia (10.5%) with CARBO was noted.

Tube dependence (gastrostomy/tracheostomy) had 2.7-fold increase in risk of death in pts (n = 25, 44%) with hypopharynx/larynx cancer, compared with stage and subtype matched pair analysis in pts < 70 yrs. Factors predicting poor PFS were ECOG (1 vs 2) HR = 0.25 (95%CI:0.90-0.70), Completion of treatment without any breaks while on CCRT, HR = 2.54 (95%CI:1.02-6.32, p = 0.04), and age in 70-75 yrs, HR = 1.09 (adjusted for alcohol and smoking) (95%CI: 1.01-1.20, p = 0.08). Factors suggestive of poor PFS were hypotension, hypercreatinemia and weight loss > 3kgs from their baseline. PFS (80%) in pts with stage III and IV disease was 22 (95%CI:12.4-87.2) months and 15.53 (95%CI: 8.6-20.6) months respectively.

Conclusions: Curative intent CCRT should be considered as standard of care in elderly patients ≥70 years with good ECOG status. Both cisplatin and carboplatin showed significant benefit in PFS with fewer side effects. Aggressive swallowing rehabilitation, abstinance from smoking and alcohol are likely to improve outcomes.

Legal entity responsible for the study: Amrita Institute of Medical Sciences

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1078P Multidisciplinary team management in head and neck cancer: The real life experience

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Background: Multidisciplinary team (MDT) management in oncology is integrated in a legal framework in France. This practice is essential in Head and Neck cancer management with its complex and multimodal treatments. Some trials report a positive impact of MDT on overall survival of advanced head and neck cancers. The objective of this study was to report the experience of MDT management in Head and Neck cancer in the Lucien Neuwirth Cancer Institute over the past 6 years.

Methods: Records from bi-monthly MDT meeting from 2010 to 2015 were selected for this study. Number of medical cases and type of present medical specialists were noted. Data from MDT records were treated: clinical characteristics (performans status, weight), anatomical localisation, TNM and pathological classification, and the treatment plan decision. Impact of MDT meeting on treatment delay was also analysed.

Results: As of December 2015, 1848 clinical cases were discussed with 1786 patients and 138 MDT meetings. Majority of patients were discussed only once in meeting, and 3% (52) patients were discussed twice. An average of 16 patient’s cases were discussed per-meeting. 1368 patients (74.1%) were presented at primo-diagnosis status and 481 (25.9%) in a recurrence status. 81% of patients were at stage III or IV. 469 (52.4%) patients had a treatment before MDT. Surgery (73.23%) was the main treatment operated before meeting. Radiation therapy delay after MDT was 9.8 days for dosimetric planification CT and 21 days for first radiation treatment session.

Conclusions: The percentage of presented recurrent patients is reasonable regarding epidemiologic data in head and neck location. MDT seems not delay radiation treatment occurring within 21 days after MDT. Unfortunately we underlined a majority of patients surgically treated before MDT discussion.
AstraZeneca, R. Galilun, M. Tahara, K. Hoermann: COI to follow all authors have declared no conflicts of interest.

1097P Long-term response to second-line afatinib in patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC): Analysis of the LUX-Head & Neck 1 (LHN1) trial


Disclosure: Clinical trial identification:

- Clinical trial: NCT02989259
- Clinical trial identification: NCT01345682

Background: In the Phase III LHN1 trial, second-line afatinib (A) significantly improved PFS (primary endpoint) vs mepatuzumab (MTX) in pts with R/M HNSCC. Tumour biomarker analyses have shown that survival benefit with A vs MTX was more pronounced in pts with p16/Erbb3-negative, EGFR-amplified, PTEN-negative disease. We present post hoc analyses of A of long-term responders (LTs).

Methods: Pts with incurable R/M HNSCC who had received first-line platinum-based therapy were randomised to A (40mg/day) or MTX (60mg/m²/week) and treated until progression/in tolerable AE. LTs were defined as pts treated with A > 12 mos. Seven tumour biomarkers were assessed by IHC (p16, Erbb3, PTEN, cMET and FISH (EGFR amplification)); pre-treatment (tx) serum samples were analysed with the VeriStat® (VS) test and classified as VN/Good/Poor.

Results: 11/323 (3%) pts treated with A were LTs with a median (range) tx-duration of 16 (12–59) mos. All pts had stopped tx at analysis. Baseline characteristics in LTs were similar to the overall dataset, except (LTs/overall): oral cavity primary tumour site (45%/29%); M1 disease (45%/66%); previous therapy with EGFR-antibodies (18%/59%); Median OS was 18.1 mos; median PFS (central independent review) was 12 mos. Tumour biomarker data allowed the evaluation of the following patterns:

- While the EXTREME protocol, including platinum (P) fluorouracil (FU) and cetuximab (Cx), is the gold-standard first line chemotherapy for metastatic head neck cancer patients (MHNC), its benefit in an unselected population has never been evaluated. Furthermore, KRAS Lcs6 variation was reported as a potential marker for greater efficacy of EGFR-targeted therapy. We investigated the benefit on progression-free survival (PFS) and overall survival (OS) of adding Cx to PFU as first line treatment for MHNC in an unselected population. We also assessed if there was a differential efficacy of Cx based on the KRAS Lcs6 status.

Methods: This monocentric retrospective study included all the patients treated by at least two cycles of PFU + Cx between 2005 and 2014 as first line palliative chemotherapy for MHNC. When tumor samples were available, the KRAS Lcs6 variant status (rs1674370) was determined by pyrosequencing, and the p16 status by immuno-histo-chemistry.

Results: 134 patients were included: 59 (44%) treated with PFU and 75 (56%) with PFUCx. Baseline characteristics were comparable between the two groups. Of note 30% of the patients had a stage 2 or 3 performance status (PS). In univariate analysis, a longer median PFS was observed with PFUCx compared to PFU (6.1 vs 4.4 months respectively, HR 0.68, p = 0.02). Median OS were not different (11.1 months with PFUCx versus 9.1 with PFU, p = 0.2). Among the 110 tumor samples available, 29 (25%) had a KRAS-variant and 14 (12.7%) were p16 positive. No differences in OS nor PFS were observed according to the KRAS-variant status. Considering only the patients treated with PFUCx, presence of the KRAS-variant (n = 17) was not associated with a better response (p = 0.5). A multivariable analysis including PS ≤ 1, addition of Cx, KRAS status, p16 status and age ≤ 55 as variables, addition of Cx to PFU was the only factor related to a better PFS (p = 0.008).

Conclusions: This retrospective study confirmed the effectiveness of the EXTREME protocol on PFS in an unselected population of MHNC patients. KRAS Lcs6 variant was not related to a differential response to Cetuximab in MHNC population.

Legal entity responsible for the study: Centre Henri Becquerel

Funding: IRON - Centre Henri Becquerel

Disclosure: All authors have declared no conflicts of interest.

1082P A pilot study of apatinib in heavily pretreated metastatic adenocarcinoma of the head and neck

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Background: Although antiangiogenic therapy is effective in advanced lung, breast, renal, hepatic, and colon cancers, limited is known about its value in the cancer of the Head and Neck. Apatinib is an oral, highly potent tyrosine kinase inhibitor targeting vascular endothelial growth factor receptor 2 (VEGFR-2). This prospective phase II study (NCT02989259) aims to investigate the efficacy and safety of apatinib in heavily pretreated patients (pts) with metastatic adenocarcinoma of the Head and Neck.

Methods: This study enrolled pts with metastatic adenocarcinoma of the Head and Neck, who failed in the metastatic setting at least one prior chemotherapy regimen. The primary end point of this study was progression-free survival (PFS). Secondary endpoints included objective response rate (ORR), disease control rate (DCR), overall survival (OS), and safety. Patients were treated with apatinib 500 mg daily. Efficacy was assessed every 6 weeks.

Results: From December 2016, we recruited 10 pts, including 8 males and 2 females, with a median age of 53 years (26-71). Median number of previous chemotherapy regimens for the metastatic disease was 2 (1-3). Median follow-up time was 4.3 months. 8 pts were eligible for efficacy analysis. ORR was 25% (2/8). DCR was 87.5% (7/8). Median PFS and median OS were not reached. The most common adverse events (AEs) of all grade were hypertension (n = 5), nausea (n = 4), fatigue (n = 4) and hand-foot syndrome (n = 3). The most common grade 3/4 AEs were hypertension (n = 2), thrombocytopenia (n = 1) and oral mucositis (n = 1). Toxicities were tolerable and manageable.

Conclusions: Our results so far indicated that apatinib exhibited objective efficacy in heavily pretreated, metastatic adenocarcinoma of the Head and Neck with acceptable safety.

Legal entity responsible for the study: Nicolas Magné

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Background: We performed a retrospective survey to study the natural history and the prognostic factors of patients (pts) with bone metastases (BM) from head and neck cancers (HNC).

Methods: Clinical records of pts treated at 11 oncologic centers across Italy were collected. Median time to first BM was 9 and 12 months for NPCs and other-HNCs, respectively. SREs occurred in 9% and 27% NPC- and other-HNC pts, respectively. SREs were associated with a poorer prognosis (not significant). Biphosphonates and/or denosumab were administered in 34% NPC and 33% other-HNC pts, respectively. The administration of bone-directed therapies, also including radiation therapy and surgery on BMs, was associated with a better survival at univariate analysis in both NPC and other-HNC (Hazard Ratio (HR) ¼ 0.39; p ¼ 0.036) and in non-oropharyngeal subpopulation (HR: 3.67; IC95%: [1.99-6.80]; p ¼ 0.001) but not in the oropharyngeal subpopulation (p ¼ 0.51). In multivariate analysis NLR >5 was significantly associated with a poorer OS in the OP (HR: 2.89; IC95%: [1.14-7.33]; p = 0.025) and in non-oropharyngeal subpopulation (HR: 4.55; IC95%: [1.43-13.5]; p = 0.014). The LR was the first independent predictor that was significantly associated with a shortened OS (p = 0.010 and 0.021, respectively). Only the BMI was found to be significantly associated with PFS (HR=0.97; p = 0.05).

Conclusions: In this cohort of patients treated with chemo-radiotherapy for head and neck cancer, pre-treatment NLR >5 was predictive of shorter overall survival. Further prospective clinical investigations are required to confirm these results and determine the clinical applicability as prognostic factor.

Legal entity responsible for the study: Centre Oscar Lambret

Funding: None

Disclosure: All authors have declared no conflicts of interest.
All authors have declared no conflicts of interest.

Background: We investigated the diagnostic and prognostic impact of plasma osteopontin (pOPN) concentrations in advanced nasopharyngeal carcinoma (NPC).

Methods: Pre-treatment plasma samples from 138 patients with previously untreated and biopsy-proven NPC were collected. Plasma samples from another 70 healthy volunteers were served as control. OPN concentrations were measured by the enzyme-linked immunosorbent assay (ELISA). The patient characteristics were: age range 24-83 and median 48 years, male/female=97/41, WHO pathology type I/II/III=1/10/52, stage III/IV(M0) (M1)= 57/73/8. The treatment consisted of radiotherapy alone (2), concurrent chemoradiotherapy (28), and neoadjuvant chemotherapy plus radiotherapy (100) for M0 patients, and systemic chemotherapy with or without radiotherapy for M1 patients.

Results: NPC patients (median 97.2 ng/mL; interquartile range 71.2-130.4) had significantly higher pOPN level than normal control (median 61.6 copies/mL; interquartile range 44.9-88.1), NPC patients (median 97.2 ng/mL; interquartile range 72.1-130.4) had significantly higher pOPN concentration and found that patients with higher pOPN (>100 ng/mL) correlated with mostly locally poor prognostic factors, such as older age, male gender, advanced T-stage, and advanced overall stage. Pretreatment pOPN affected patients’ survival as well as rate of distant failure. The 5-year overall survival (56.6% vs. 81.4%, P=0.0036) and metastasis-free survival (66.3% vs. 81.2%, P=0.0726) were significantly lower in patients with pretreatment pOPN > 100 ng/mL than in those with pOPN ≤ 100 ng/mL.

Conclusions: Pretreatment pOPN levels can serve as a useful diagnostic and prognostic marker for advanced NPC.

Legal entity responsible for the study: Taichung Veteran General Hospital

Funding: All authors have declared no conflicts of interest.

Disclosure: All authors have declared no conflicts of interest.

1089P

GSTP1 c.313AG, XPD c.934GA, XCF c.2505TC and CASP9 c.-1339AG polymorphisms and severity of vomiting in head and neck cancer patients treated with cisplatin chemotherapy


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Background: Cisplatin (DDP) chemotherapy associated with radiation (RT) has been used in head and neck squamous cell carcinoma (HNSCC) patients, and vomiting is a common side effect during treatment. This prospective study aimed to identify the roles of GSTT1 and GSTM1 (presents or nulls), GSTP1 c.313AG, XPD c.934GA and XCF c.2505TC polymorphisms and severity of vomiting in head and neck cancer patients treated with cisplatin chemotherapy.

Methods: We evaluated 88 HNSCC patients diagnosed June 2011–February 2014 which received CDDP chemoradiation. Ondansetron and dexamethasone were administered in HNSCC patients treated with CDDP and RT. Randomised clinical trials describe the benefit of chemotherapy for specific head and neck patients with selected patient and tumour characteristics. This study estimates the overall survival benefit of chemotherapy above all other modalities for the whole population of head and neck cancer patients in Australia, if evidence-guidelines were followed.

Conclusions: First-course chemotherapy improved population-based survival in head and neck cancer patients, and used in accordance with guidelines recommendations. Measurement of population survival benefit of cancer treatment is important as this can provide salient inputs for economic analyses, aid in priority setting in cancer program and guide quality improvement according to evidence-based guidelines.

Legal entity responsible for the study: CCORE, Ingham Institute for Applied Medical Research, Sydney, Australia

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1086P

Diagnostic and prognostic impact of plasma osteopontin in nasopharyngeal carcinoma

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Background: We investigated the diagnostic and prognostic impact of plasma osteopontin (pOPN) concentrations in advanced nasopharyngeal carcinoma (NPC).

Methods: Pre-treatment plasma samples from 138 patients with previously untreated and biopsy-proven NPC were collected. Plasma samples from another 70 healthy volunteers were served as control. OPN concentrations were measured by the enzyme-linked immunosorbent assay (ELISA). The patient characteristics were: age range 24-83 and median 48 years, male/female=97/41, WHO pathology type I/II/III=1/10/52, stage III/IV(M0) (M1)= 57/73/8. The treatment consisted of radiotherapy alone (2), concurrent chemoradiotherapy (28), and neoadjuvant chemotherapy plus radiotherapy (100) for M0 patients, and systemic chemotherapy with or without radiotherapy for M1 patients.

Results: NPC patients (median 97.2 ng/mL; interquartile range 71.2-130.4) had significantly higher pOPN level than normal control (median 61.6 copies/mL; interquartile range 44.9-88.1), NPC patients (median 97.2 ng/mL; interquartile range 72.1-130.4) had significantly higher pOPN concentration and found that patients with higher pOPN (>100 ng/mL) correlated with mostly locally poor prognostic factors, such as older age, male gender, advanced T-stage, and advanced overall stage. Pretreatment pOPN affected patients’ survival as well as rate of distant failure. The 5-year overall survival (56.6% vs. 81.4%, P=0.0036) and metastasis-free survival (66.3% vs. 81.2%, P=0.0726) were significantly lower in patients with pretreatment pOPN > 100 ng/mL than in those with pOPN ≤ 100 ng/mL.

Conclusions: Pretreatment pOPN levels can serve as a useful diagnostic and prognostic marker for advanced NPC.

Legal entity responsible for the study: Taichung Veteran General Hospital

Funding: All authors have declared no conflicts of interest.

Disclosure: All authors have declared no conflicts of interest.

1087P

Head and neck cancer (HNC) and synchronous lung cancer: Impact of the lung cancer on the management and prognosis of these patients. Data from the SYNCHRON GFPC 15-04 Study

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Background: Management of synchronous head and neck and lung cancer is almost difficult. The aim of this observational study was to describe the impact of the lung cancer on the management and prognosis of HNC.

Methods: Inclusion criteria: consecutive patients diagnosed between January 2011 and December 2015 in 19 French centers with HNC and synchronous lung cancer (all stages). We describe: clinical characteristics, management and outcomes. Patient characteristics and treatment information was analysed and descriptively. Kaplan-Meier estimation was used to assess median overall survival.

Results: The study included 132 patients: men 83%, 63.7 years old, current smokers: 59.8%, performance status: 0 and 1 for 22% and 66% of the patients respectively; high rate of comorbidities: cardiovascular: 63%, COPD: 33%. Main histology for HNC was squamous: 98% (in oral cavity: 24%, oropharyngeal: 26%, hypo-pharyngeal: 22% and laryngeal: 28%) T classification: T1: 0, T2: 23, T3: 74 and T4 in 16%, 24%, 28% and 14% of cases respectively, and N classification was N0, N1, N2, N3, for 36%, 18%, 20% and 8% of cases respectively. The main treatment was surgery, 37.1%, and chemoradiotherapy, 35.6%. The diagnosis of lung cancer impacts the HNC management in 38% of the cases. Median delay between HNC and first treatment was surgery, 28.3 days. Pretreatment pOPN affected patients’ survival as well as rate of distant failure. The 5-year overall survival was 35% at 2 years. OS was 40% at 2 years, better for stage I-II lung cancers (55%).

Conclusions: Synchronous lung cancer at HNC diagnosis significantly impacts the management and outcomes of HNC. Specific recommendations and multidisciplinary approach should be elaborated to improve the management of these patients.

Legal entity responsible for the study: Groupue Français de Pneumo-cancérologie

Funding: Boringier Pierre Fabre

Disclosure: All authors have declared no conflicts of interest.

Annals of Oncology
Background: The objectives are to define the characteristics of people with HNSCC treated in our area and quantify the impact of the committee on the staging, the change in the initial treatment proposed to determine whether the selection of treatment by the multidisciplinary team (MDT) influences therapeutic compliance.

Methods: Observational retrospective study of two cohorts, which aims to analyze the variables in the cohort of patients handeled by an MDT with respect to the patients without an MDT. We included all patients with an initial diagnosis of HNSCC at our centre between 2005 and 2012. The MDT cohort comprised those from 01/01/2009 to 31/12/2012. With access to the Pathological Anatomy database, the records of the MDT, the archived and computerised medical history, we collected the endpoints related to the patient (age, sex, eCOG), the tumour (date of diagnosis, location, and TNM stage), the treatment (therapy selected, change in treatment, compliance, reason for default).

Definitive sample consists of 408 patients. A descriptive analysis is given of the clinical characteristics of the sample, together with the comparative bivariate analysis of these characteristics in the cohorts.

Results: Our population presents age (median) 64.2y (SD 12.4), male 82.6%, eCOG <2 69%, 32.1% laryngeal location, tumour stage IVA 31.6%, Treatment with S 43.4%, and radiotherapy (RT) 14.7%, RT 10% and chemo-radiotherapy 9.8%. From our comparative analysis we want to highlight (1) vs C2 change in stage 26 vs 19.7%, increase 1.5 vs 15.4% (< 0.001), change of treatment 34.5 vs 39.9% (< 0.001), organ-preservation without surgery 3 vs 6.3% (< 0.001) and therapeutic compliance 91 vs 92.3% (p = 0.72).

Conclusions: The population served in our area presents clinical characteristics similar to those of other series published in our and other countries. The MDT improved the staging of the tumour before treatment in a statistically significant way. The change in treatment is higher, so as to be statistically significant, when the therapeutic planning is addressed by an MDT. No statistically significant difference was observed in therapeuetic compliance rates when treatment was decided by the MDT.

Legal entity responsible for the study: María José Martínez-Ortiz

Funding: None

Disclosure: All authors have declared no conflicts of interest.

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Table: 1091P The Prognostic Nutritional Index (PNI): definition

<table>
<thead>
<tr>
<th>Score</th>
<th>Definition</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 points</td>
<td>PNI &gt; cutoff = PNI-high group</td>
<td>Normal nutritional status - Low risk</td>
</tr>
<tr>
<td>1 point</td>
<td>PNI &lt; cutoff = PNI-low group</td>
<td>Moderate severe nutritional impairment - High Risk</td>
</tr>
</tbody>
</table>

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Results: At baseline, HPV pts were younger with a median age of 54.5 (41-59 years) vs 60.6 (43-77 years) and with less advanced stage (stage III 18.8% vs 20.5%; stage IVa 78.1 vs 62.1%; stage IVB: 3.1% vs 17.2%). The optimal cutoff established in the HIV set was 45. According to this cutoff, 10 pts (20%) in HIV set had a low PNI. In HIV set, OS at 12-months follow-up (FU) was 79% in PNI-high group vs 37.5% in PNI-low group (P = 0.032) with a Hazard ratio (HR) of (1.0) of 2.84 (95%CI 1.04-7.78) in the multivariate analysis.

In the HIV set, a low PNI was found in 23 (26.4%) out of 87 pts. OS at 12-months FU was 99% in PNI-high group and 45% in PNI-low group (p = 0.007) with a HR of 3.9 (95% CI 1.45-10.98) in the multivariate analysis.

Conclusions: PNI is a valuable prognostic marker in LAHNSCC associated with survival in pts treated with ICT followed by CCRT. PNI could be useful for stratification in future clinical trials.

Clinical trial identification: None

Legal entity responsible for the study: Gema Bruzualo

Funding: None

Disclosure: All authors have declared no conflicts of interest.

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Table: 1093P Resource-stratification of national comprehensive cancer network (NCCN) head and neck cancers guideline

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Background: Resource constraints in low- and middle- income countries (LMICs) often impede critical medical care. 65% of new cases of lip and oral cancer, and 76% of related deaths occur in LMICs, where patients lack access to standard diagnostic tests and/or treatment approaches. The development of resource-stratified clinical guidelines promotes access to critical diagnostic and treatment pathways in LMICs.

Methods: To address the unmet need in LMICs, a multi-disciplinary committee of NCCN Member Institution experts developed the NCCN Framework1 for Head and Neck Cancers. Lip and Oral. In the evidence-based, resource-stratified Guidelines, recommendations from the NCCN Guidelines for Head and Neck Cancers were assigned to specific resource levels, based on access to various interventions and importance in

Disclosure: All authors have declared no conflicts of interest.
achieved clinical outcomes. International experts reviewed the resource-stratified Guidelines to assess utility in LMICs and NCCN approved and published the finalized guidelines.

**Results:** The NCCN Framework for Head and Neck Cancers: Lip and Oral has four resource levels: Basic, Core, Enhanced, and Parent guideline. The Framework for Basic Resources identifies essential services required for minimal standard of care for improvement in outcome; the Core Resources lead to improved outcomes but are not cost prohibitive; the Enhanced Resources recommend additional services that may improve outcomes, but may be cost prohibitive in certain settings. For initial treatment of early stage cancer of the oral cavity (T1-2, N0) as an example, the Enhanced Framework recommends surgical resection and radiation therapy (RT), but not sentinel lymph node (SLN) biopsy, which is recommended in the NCCN parent Guidelines and requires more advanced resources. The Basic Framework recommends surgical resection as the only primary treatment option, since RT may not be available at this resource level.

**Conclusions:** The NCCN Framework for Head and Neck Cancers: Lip and Oral provides LMICs with a system to optimize care in limited resource settings, and a map to improve cancer care incrementally as resources become available. Use of this framework facilitates improved patient care in resource-constrained settings.

**Legal entity responsible for the study:** National Comprehensive Cancer Network

**Funding:** None

**Disclosure:** All authors have declared no conflicts of interest.

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**1094P Long-term results of chemoradiotherapy for stage III nasopharyngeal carcinoma patients and risk grouping by pretreatment EBV viral load**

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**Background:** No previous study reported the treatment outcome of stage III nasopharyngeal carcinoma (NPC) patients. The aim of this study is to investigate the long-term clinical outcome of stage III NPC patients and risk grouping by plasma EBV DNA assay for future therapy improvement.

**Methods:** A total of 356 previously untreated, pathologically-proven NPC patients with stage III disease and available pretreatment plasma EBV DNA data were enrolled in this retrospective study. Initial definitive treatment consisted of concurrent chemoradiotherapy or induction chemotherapy plus radiotherapy. Eighty-four of 356 (23.6%) patients also received post RT adjuvant chemotherapy. Patients with pretreatment EBV DNA > 1000 copies/mL were defined as a high-risk subgroup (n=106) and the remaining patients as a low-risk subgroup (n=250).

**Results:** After a median follow-up of 90 months, there were 66 recurrences (18.5%) and 57 deaths (16.0%). The 5-year overall survival (OS), progression-free survival (PFS), and distant metastasis-free survival (DMFS), and locoregional failure-free survival (LRFFS) for all 356 patients were 88.4%, 83.9%, 90.5%, and 90.5%, respectively. Thirty-five of 106 (33.0%) high-risk patients developed tumor relapse later, whereas only 12.4%(31/250) low-risk patients had tumor relapse (P<0.001) Survival analysis revealed that the high-risk subgroup had significantly worse OS (5-year rate, 79.6 vs. 92.8%, P=0.001), PFS (73.7 vs. 88.4%, P<0.0001), DMFS (88.2% vs. 95.0%, P<0.0001), and LRFFS (85.6% vs. 92.6%, P=0.0005) than those of the low-risk subgroup.

**Conclusions:** Long-term treatment results for Stage III NPC patients were good. Risk grouping identified a subgroup of patients with high pretreatment EBV DNA load that may significantly higher relapse rates and worse survivals. Future trial should strengthen treatment intensity for these high-risk patients.

**Legal entity responsible for the study:** Taichung Veterans General Hospital

**Funding:** Taichung Veterans General Hospital

**Disclosure:** All authors have declared no conflicts of interest.

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**1095P Nasopharyngeal cancer in children: Long term results the experience of the university hospital of Sfax (Tunisia)**

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**Background:** Nasopharyngeal carcinoma in children is frequent in Mediterranean area. We aimed to report our experience in the treatment of this entity.

**Methods:** We retrospectively review the records of 76 young patients (<21 years) presenting with nasopharyngeal cancer during the period 1993-2015. Diagnosis was confirmed with histological study of the biopsy of nasopharynx. Initial work-up included nasoendoscopy, CT scan and/or MRI of the nasopharynx and neck, chest X-ray, abdominal ultrasonography and bone scan. TNM 2009 classification was used. Patients treated before 2009 were retrospectively reclassified. Metastatic patients were excluded. Patients had cisplatin based regimen chemotherapy (neoadjuvant, concomitant or both). Radiotherapy was delivered at the dose of 70 to 75 Gy targeting the nasopharynx and involved cervical nodes. Prophylactically done up to 50 Gy was delivered to the remaining cervical areas. Survival was studied with Kaplan Meier test. Late toxicities were assessed according to SOMA-LENT and RTOG scales in patients with a minimal follow-up of >24 months.

**Results:** Mean age was 16 years (9-20). Sex-ratio was 1.1. Seventy two percent of patients (n=55) had locally advanced tumor (T3 or T4). Cervical nodal involvement was seen in 2009% of cases (n=71). There were 52 cases (68%) of N2 or N3. Sixty-six patients had no Enhanced Resources and 5 had both. Five patients had exclusive irradiation. Radiotherapy was monofractionated in 45 cases and bifractionated in the remaining cases. Acute toxicities were tolerable. Mean follow-up was 198 months (28-289). One patient experienced a local failure. Twenty-six presented metastatic failures. Overall survival rate at 10 years is 67.4%. Disease free survival rate at 10 years is 66.7%. Xerostomia was the most frequent late toxicity (97%). Patients experienced endocrine troubles (hypothyroidism in 19%, amenorrhea in 13%), cerebral necrosis (Seizures), osteoradonnosis (18 cases) and secondary cancer (3 cases).

**Conclusions:** Pediatric nasopharyngeal carcinoma has good prognosis despite frequent locally advanced disease at presentation. Combining radiotherapy and chemotherapy is the standard of care. Late toxicities are often severe and affect the quality of life.

**Legal entity responsible for the study:** University Hospital of Sfax - Tunisia

**Funding:** None

**Disclosure:** All authors have declared no conflicts of interest.

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**1099P Incidence and impact of DPD mutation on neoadjuvant chemotherapy in head and neck cancers**

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**Background:** Dihydropyrimidine dehydrogenase (DPD) is an enzyme essential for metabolism of 5FU. The incidence of polymorphisms or mutation in variable across different ethnic populations. This study is first report highlighting the high incidence of DPD mutation is seen in head and neck cancers in India.

**Methods:** Consecutive patients with head and neck cancer undergoing TP neoadjuvant chemotherapy at our centre between May 2015 - December 2016 underwent DPD mutation analysis. The haematological toxicities consisting of neutropenia and thrombocytopenia while gastrointestinal toxicities consisting of mucositis and diarrhea were considered as SFU related toxicities for this analysis. Toxicities were graded in accordance with CTCAE (Common Terminology Criteria for Adverse events version 4.0). DPD mutation analysis by Sanger sequencing on ABI 3500 platform, for the most prevalent exonic regions (Exon 13 - c1672T>A (GDPD5)*V14347A (ATA> GTA); Exon 14 – 1450G>T; (G615D) missense mutation, Exon 14 splice variant G>A and Exon 18 (DPD6) (p237)/c-2194G>A (GTT>ATT)). Descriptive statistics was performed using SPSS version 16 and RStudio. Proportions with 95% CI were described. Fisher’s exact test was performed to see the relationship between DPD mutation status and grade 3-5 adverse events.

**Results:** Consecutive 118 patients were included in this analysis. The median age was 45 years (IQR 37.25-54.00) years. The median cycles of TPF received were 4 (range 1-6). DPD mutation was seen in 25 patients (24.59%, 95%CI 16.94-32.23%). The mutations were seen in exon 18 in 17 patients (14.4%), exon 13 in 9 patients (7.6%) and in both exon 13 & 18 in 3 patients (2.5%). 100 patients were eligible for assessment of adverse events (84.7%). The rate of grade 3-5 haematological and gastrointestinal adverse events was 64% and 35% respectively. The rate of grade 3-5 haematological (88.5% versus 55.4%, p=0.012) and gastrointestinal adverse events (57.7% versus 27.0%) were higher in DPD mutated cohort.

**Conclusions:** This study signifies the importance of ethnic difference in drug polymorphisms and mutations. The impact of these adverse events in DPD mutated patients justifies doing a DPD mutation prior to subjecting patient to 5FU in head and neck cancer.

**Legal entity responsible for the study:** Tata Memorial Hospital Centre, Mumbai

**Funding:** None

**Disclosure:** All authors have declared no conflicts of interest.

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**1099P Radiotherapy related xerostomia in head and neck oncology: A systematic review**

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**Background:** Radiotherapy in the head and neck region can lead to salivary gland hypofunction and as a result dry mouth ensues. We have undertaken this systematic review and meta-analysis to estimate the effectiveness of available interventions for radiotherapy-induced xerostomia and hyposalivation.

**Methods:** A systematic review and meta-synthesis techniques were adopted to identify, appraise and synthesize the relevant literature regarding the experience of nutritional symptoms of HNC patients conducted according to the PRISMA guidelines. Several...
Conclusions: Addition of HMB/Arg/Gln to opioid-based pain control and oral care events related to HMB/Arg/Gln were increase in blood urea nitrogen and diarrhea, but 80.0% at 2 weeks and 100% at 4 weeks after completion of RT. Only 5.7% of patients programs was feasible but still insufficient in reducing the incidence of severe CRT-related MTM.

Legal entity responsible for the study: nil

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1100P The phase II study of HMB/Arg/Gln against oral mucositis induced by chemoradiotherapy for head and neck cancer patients

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Background: Opioid-based pain control and systemic oral care program are effective for the chemoradiotherapy (CRT)-induced severe oral mucositis (OM) in patients with head and neck cancers (HNC). This phase II trial assessed the clinical benefit of beta-Hydroxy-beta-Methylbutyrate, Arginine, and Glutamine (HMB/Arg/Gln) in the prevention of CRT-induced OM in patients with HNC.

Methods: Patients with HNC who were scheduled to receive definitive or postoperative cisplatin-based CRT were enrolled. HMB/Arg/Gln was administered orally or per oraglasia. The use of other treatment modalities cannot be supported on the basis of current evidence.

Legal entity responsible for the study: nil

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1100P Sinonasal non-glandular cancers relapsing after multimodal treatments

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Background: Multimodality treatment (MMT) is the current approach to advanced sinonasal cancer (SC). We lack salvage treatment standardization especially for pts already receiving MMT. No clinical factors able to predict outcome have been identified in this disease setting.

Methods: We retrospectively analyzed a series of pts with recurrent/metastatic (RM)-SC after multimodal curative treatment, consisting in induction chemotherapy (IC) followed by locoregional therapy. Overall survival (OS) was measured as the interval from relapse to death.

Results: Among 106 pts with SC treated with MMT at our Center from 1997 to 2016, 50 (M/F 31/19) relapsed. Median age was 53 yrs (16-73). Median follow-up was 26 months (m) (5-192). WHO 2005 histotypes were: 36% sinonasal undifferentiated carcinoma (SCUC), 34% squamous cell cancer (SCC), 30% carcinomas with neuroendocrine differentiation (CND). Median time to first relapse after curative treatment was 13.5 m. Median OS was 13 m from recurrence: 19 m in SCC, 16 m in SCUC and 6 m in CND (p = .34). Relapse occurred as distant metastasis in 49%, as nodal recurrence in 6% and at primary site in 34% of cases. First line salvage treatment was surgery in 38% (14 pts received surgery on T, 2 on N and 3 on M), CT in 30%, RT in 8%, best supportive care in the remaining pts. Median OS was 31 m in surgically treated pts and 4.8 m in those receiving CT (p < .001). In pts with disease control (PR + SD) after iCT, median OS after recurrence was longer than in pts with PD (13.4 vs 1.5 m, p < .002). Pts with an objective response to palliative CT had a longer median OS than those with PD (20 vs 4 m, p = .002).

Conclusions: Prognosis of SC relapsing after MMT is dismal. With the caveat of a retrospective analysis and a case series that has been collected in a long time frame, we showed that feasibility of salvage surgery; objective response to prior definitive treatment and response to palliative CT are factors associated with better outcomes. Pts with relapsed or metastatic SC not amenable to salvage surgery should be considered for enrolment in clinical trials.

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale Tumori

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Background: Histological grade is the most important factor for defining treatment strategies and predicting prognosis for salivary gland carcinoma (SGC). Although several studies have addressed low- and high-grade SGCs, intermediate-grade SGC (IGSGC) has received minimal attention. Therefore, we examined factors affecting long-term recurrence and survival among IGSGC patients to define optimal treatment modalities and outcomes.

Method: We reviewed the clinical and pathological data of 108 IGSGC patients who underwent definitive surgery with or without postoperative radiotherapy at our tertiary referral center between 1994 and 2014. We performed univariate and multivariate analyses of variables predictive of locoregional control (LRC), distant metastasis-free survival (DMFS), and overall survival (OS) (28). We identified treatment outcomes by treatment strategies such as surgical extent, primary tumor, neck dissection, or postoperative radiotherapy.

Results: During a median 103 (range, 24–282) month follow-up, local, regional, and distant recurrences were detected in 14 (13.0%), 3 (28), and 21 (19.4%) patients, respectively. The 10-year LRC, DMFS, and OS rates were 83.1%, 70.8%, and 80.1%, respectively. Multivariate analysis identified a primary non-salivary primary site as an independent prognostic factor for OS (P = 0.018). Adenoid cystic carcinoma and positive pN classification were significantly unfavorable prognostic factors for DMFS (P = 0.025 and P = 0.030, respectively); overall advanced stage was an independent prognostic factor for OS (P = 0.002). Surgical extent, elective neck dissection, and postoperative adjuvant radiotherapy did not significantly affect treatment outcomes.

Conclusions: Patients with early-stage IGSGC of parotid origin can achieve favorable treatment outcomes with conservative surgery alone.

Legal entity responsible for the study: no

Funding: None

Disclosure: All authors have declared no conflicts of interest.
by demonstrating a 15% improvement in Progression Free Survival (PFS) rate at 6 months in favor of ADT.

**Trial design:** In this multicenter, randomized, phase II intergroup study a total of 76 treatment naïve patients (Cohort A) are planned to be randomized to receive ADT or platinum-based chemotherapy. Previously treated patients will be enrolled in a separate Cohort B to receive ADT. Patients from Cohort A randomized to chemotherapy can also enter Cohort B at disease progression. The primary endpoint is PFS for Cohort A and best overall response for Cohort B. Central testing of AR expression is based on staining intensity (0 = negative, 3 = strong) and percentage of positive nuclear stained cells (0 = ≤10% to 3 = ≥70%). AR overexpression requires a maximum score of 3 on both scales. Mechanisms of AR activation and resistance will be studied. This study is led by EORTC Head and Neck Cancer Group with UNICANCER/RECOR, International Rare Cancer Initiative UK Salivary Gland Cancer Group and RARECARENet. It will run in 35 sites in 10 countries: Austria, Belgium, France, Germany, Greece, Hungary, Italy, Portugal, The Netherlands, and United Kingdom. Sites from the EURACAN European Reference Network are participating. Currently, 36 patients are registered; 20 have AR overexpression, of which 16 have been randomized in Cohort A. Identification of AR as a treatment target in SGC can be practiced analyses (e.g. CYP17 expression; PI3K mutations). Blood and saliva samples will be obtained from patients after surgery of cisplatin 100 mg/m² (every 3 weeks; 3 cycles) to radiotherapy. The population is defined as patients with radioresistant histologies (e.g. cystic adenoids carcinomas) or patients with unfavorable prognostic criteria (e.g. incomplete resection, T4 tumor, malignant lymph node(s) with capsular rupture, presence of emboli, ...). The primary endpoint is the progression free survival. Secondary outcomes are: overall survival, quality of life, time to progression (locoregional and distant) and toxicities. Two hundred and sixty patients will be enrolled in 5 years. Eligible patients are adults, with a performance status ≤2 and an adequate hematological and renal function for capcitabine treatment. Recruitment is ongoing in France. The study comprises a quality assurance program in radiotherapy and surgery. Coordinating investigators are Drs Ferrand and Thariate.

**Clinical trial identification:** NCT01969578.

**Legal entity responsible for the study:** European Organization for Research and Treatment of Cancer

**Funding:** EORTC ICR RARECARENet Fondazione IRCCS Istituto Nazionale dei Tumori

**Disclosure:** All authors have declared no conflicts of interest.
Trial design: Patients aged ≥ 18 yr with histologically confirmed SCC of the oral cavity, oropharynx, larynx or hypopharynx, previously untreated, with indication of induction chemotherapy will be eligible. The primary objective is to determine the recommended Phase 2 dose (RP2D). The secondary objectives are to document any antitumor activity (PFS, ORR, RECISTv1.1 criteria), to estimate the pharmacokinetic parameters of durvalumab, to explore the relationships between immune capacity, specificity, activation state and clinical outcome. The study will be conducted in 2 parts: a dose-deescalation part to determine the RP2D (6 pts), and an expansion part (30 pts). The durvalumab will be administered every 3 weeks for 3 injections at week 1, 4, 7. The durvalumab first dose level is 1120 mg and the dose level -1 is 750 mg Q3W. The chemotherapy will be administered every 3 weeks at week 1, 4, 7 at the following doses: Docetaxel 75mg/m² on D2, Cisplatin 75mg/m² on D2, 5 Fluorouracil 750mg/m²/day from D2 to D6.

Clinical trial identification: NCT 02997332 Eudract number 2015-004146-25

Legal entity responsible for the study: Gustave Roussy

Funding: INCA and ARC Acknowledgement to Astra Zeneca for providing the drug

**Health Economics**

**1111PD Economic burden of cancer patients and the job assistance from the society**

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**Background:** Cancer patients who face the financial difficulties and are obliged to retire for the treatment are increasing in number. It is urgently important that they keep working to receive the optimal treatment. We investigate the actual situation of the patients who retired for treatment and examine the feasible measures including the desirable balance of work and treatment.

**Methods:** The cancer patients and the attending doctors were surveyed in 40 cancer centers, university hospitals and regional hospitals in Japan.

**Results:** The number of replies from patients was 3,204. The ratio of patients who were at work before treatment was 50.7%. The ratio of employees was 89.7%. Of these, 31.8% of patients quit their work for treatment. It was as high as the 38.7% in lung cancer, and as the lowest as 27.1% in breast cancer. In case of retirees, the ratios of stage I, II, III and IV were 20.6%, 17.9%, 13.9% and 43.7% respectively. The ratio of stage IV was 26.8% in the whole patients, and therefore the retirees tend to be higher in stage IV. The annual out-of-pocket expense and including direct and indirect expense in the retirees was an average of 6,640 EUR. This was slightly smaller than that of the whole patients. The ratios of patients who felt heavy about the economic burden were 73.7% in retirement, 59.9% in the whole patients. 7% of retirees and 5.3% of the whole patients had to change or abandon the most suitable treatment due to the economic reasons. 58.5% of retirees answered that the income was decreased during the cancer treatment and this was significantly higher than that of the whole patients. The percentage of retirees whose tax-included annual income was less than 24,200 EUR was 46.4%. This was 39.2% in the whole patients. 46.7% of retired employees had no choice but to quite the work, while 42.7% answered that they wanted to continue their work.

**Conclusions:** One of three patients with cancer is in a working generation, and it is important for patients to balance the treatment with the work. It became clear in the survey that one third of the patient who was working was obliged to retirement. In most of the cases, the Cancer Control Act was revised in December, 2016 and it became the efforts of the company to continue the employment of cancer patients.

**Legal entity responsible for the study:** Nobuo Koinuma

**Funding:** Ministry of Health, Labor and Welfare

**Disclosure:** All authors have declared no conflicts of interest.

**1113PD Using the ASCO’s quality oncology practice initiative (QOPI) metrics and standards to improve value, meaningful use of resources and reduce waste**

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**Background:** The Institute of Oncology (IOV) is using the ASCO’s QOPI since 2013 in Brazil. QOPI is a retrospective analysis by data abstraction submitted to a database publishing over 180 quality measures based on care guidelines and expert consensus. Data collection are twice a year and provides reports based on practice wide data sample comparing overall quality score for the practice and for the participants aggregate.

**Methods:** IOV participates in rounds at least once a year. At each round current performance is reviewed and select gaps are translated into improvement projects that focus on meaningful use of resources, safety, accountability of care, and value. Meaningful use of PET-CT, lab tests, and G-CSF are samples of specific projects the past. IOV’s Patient Navigation System (PNS) was adapted to track QOPI standards/measures that are monitored by clinical navigators as checkpoints in real time transitions of care and handovers. Potentially hazardous checkpoints are actively chased using a daily signaling process.

**Results:** Between Feb/2016 and Mar/2017, the PNS checked 9,372 patient interactions (surgery, exams, outside appointments, optimal sequencing of care), 138 (1.5%) potentially hazardous events were identified, missing “readiness to care data” and lab tests (36%), delayed radiation or chemo (38%), delayed surgery (7%), and missing echocardiogram for patients using cardiac drugs (6%). The Pain Management Navigation System was created to meet another set of QOPI standards that also translated into 17% reduction of emergency room admissions for 141 patients involved. A dedicated flow was created to meet oral chemo standards, and patient satisfaction improved from 67% to 93% by reducing door-to-door time from 40 to 12 minutes, including check in, interview, drug refill and reconciliation.

**Conclusions:** One of the big challenges of healthcare is how to introduce changes that translates into real improvements. The use of evidence-based measures and standards to evaluate quality of care provides a clear and straight path to deliver higher value, meaningful use of resources; focus and alignment for improvements initiatives where it matters most; patient care and outcomes.

**Legal entity responsible for the study:** Instituto de Oncologia do Vale

**Funding:** None

**Disclosure:** C.F. Pinto: Board Member at Instituto of Oncology. All other authors have declared no conflicts of interest.

**References:**

Background: The objective of this study is to evaluate the cost-effectiveness of nivolumab-ipilimumab (NIVO-IPI) versus existing treatments in first-line treatment of patients with advanced melanoma from a US payer perspective using recently reported 28-month survival data from the CheckMate 067 phase III trial.

Methods: This three-state partitioned survival model was developed from projections of overall survival (OS) and progression-free survival (PFS) based on a network meta-analysis that considers time-varying hazard ratios to estimate accrued quality adjusted survival, total drug acquisition, follow-up, and toxicity costs over a lifetime time horizon (30 years). Competing treatments included NIVO, IPI, pembrolizumab (PEM), dabrafenib plus trametinib (DAB+TRA), DAB, vemurafenib plus cobimetinib (VEM+COB), VEM, and dacarbazine (DTIC). Costs and adverse event frequencies were obtained from expert input, publicly available sources, and literature. Utility weights were estimated from the CheckMate 067 trial. Incremental cost-utility ratios (ICURs) for NIVO-IPI are calculated as a 3.5% discount rate is applied to costs ($US 2016) and utilities.

Results: NIVO-IPI is projected to have the greatest accrued survival among the competing treatments with 6.012 LY and 4.979 QALY and also the highest costs ($291,096 including treatment acquisition, follow-up, management of adverse events, and post-progression costs) over the 30-year time horizon. Pairwise ICURs for NIVO-IPI versus other treatments ranged from $34,774 per QALY (vs. DAB+TRA) to $92,624 per QALY (vs. NIVO). In extended dominance analysis, DTIC, NIVO, and NIVO-IPI form the cost-effectiveness frontier, showing that these are the most cost-effective options at different willingness to pay thresholds. Probabilistic sensitivity analysis generated results consistent with the base case for NIVO-IPI.

Conclusions: The large survival gains of NIVO-IPI make it a cost-effective option for first-line treatment of advanced melanoma when compared to other immune-oncology therapies, targeted agents, and chemotherapy.

Clinical trial identification: Cost study based on the 067 trial NCT01844505 protocol number is CA209-067 (CheckMate 067)

Legal entity responsible for the study: Bristol-Myers Squibb

Funding: Bristol-Myers Squibb

Disclosure: J. Sahater, K. Gupta-Singh, S. Katopati, S. Rao; Employed by Bristol-Myers Squibb and owns stock in Bristol-Myers Squibb. T. Baker: ICON is contracted to undertake the nivolumab analysis for Bristol-Myers Squibb and ICON pays me as a consultant to the project. V. Paly: Outside of support received from Bristol-Myers Squibb in preparation of the core model and market specific adaptations. A. Briggs: ICON is contracted to undertake the nivolumab analysis for Bristol-Myers Squibb and ICON pays me as a consultant to the project. All other authors have declared no conflicts of interest.

Palbociclib in advanced breast cancer: A cost-utility analysis

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Background: The addition of palbociclib to letrozole improves progression free survival (PFS) and response rates compared to letrozole alone in the first-line treatment of hormone receptor positive advanced breast cancer (ABC). This study assesses the cost-utility of palbociclib from the Canadian healthcare payer perspective.

Methods: To evaluate the cost-utility of palbociclib, a probabilistic discrete event simulation model was developed. The model was parameterized with data from the phase 2 and 3 PALOMA 1 and 2 trials and other sources. The incremental cost per quality-adjusted life-month (QALM) gained for palbociclib was calculated. A time horizon of 15 years was used in the base case with costs and effectiveness discounted 5% annually. The time to progression and death were derived from Weibull and exponential distributions, respectively. Expected costs were based on Ontario fees and other sources. Probabilistic sensitivity analyses were conducted to account for parameter uncertainty.

Results: Compared to letrozole alone, the addition of palbociclib provided an additional 14.7 QALM at an incremental cost of $61,508. The resulting incremental cost-effectiveness ratio was $10,999/QALM gained. Assuming a willingness to pay (WTP) of $11,667 per QALM, the addition of palbociclib was not cost-effective and the probability of palbociclib to be cost-effective was 0%. Cost-effectiveness acceptability curves derived from a probabilistic sensitivity analysis showed that at a WTP of $11,667/QALM gained, the probability of palbociclib to be cost-effective was 50%.

Conclusions: Compared to letrozole alone, the addition of palbociclib is unlikely to be cost-effective for the treatment of ABC from a Canadian healthcare perspective with its current price. While ABC patients derive a meaningful clinical benefit from palbociclib, considerations should be given to increase the WTP threshold and reduce the drug pricing, to render this strategy more affordable. Model validation and calibration are needed to confirm these results.

Legal entity responsible for the study: Jacques Raphael

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Table: 1117P Milestone Overall Survival, %

<table>
<thead>
<tr>
<th></th>
<th>1L n = 356</th>
<th>2L n = 107a</th>
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<tbody>
<tr>
<td>12 mo</td>
<td>40%</td>
<td>37%</td>
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<tr>
<td>24 mo</td>
<td>37%</td>
<td>17%</td>
</tr>
<tr>
<td>36 mo</td>
<td>21%</td>
<td>5%</td>
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<tr>
<td>GemCi5</td>
<td>65% vs 52%</td>
<td>—</td>
</tr>
<tr>
<td>12 mo</td>
<td>40% vs 34%</td>
<td>—</td>
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<tr>
<td>36 mo</td>
<td>20% vs 21%</td>
<td>—</td>
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<tr>
<td>Vinflunineb</td>
<td>38% vs 37%</td>
<td>—</td>
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<tr>
<td>12 mo</td>
<td>—</td>
<td>20% vs 16%</td>
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<tr>
<td>36 mo</td>
<td>—</td>
<td>9% vs NA2</td>
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1A total of 368 pts were included; shown here are 356 pts who initiated 1L tx and 107 pts who initiated 2L tx during the study (2009-2016). 88.8% (n = 95) of the 107 pts are a subset of the 356 pts who initiated both 1L and 2L during the study.
2Most common tx per line of therapy.
3Estimate could not be calculated due to insufficient follow-up time

Conclusions: Outcomes in advanced UC tx in pts in this large real-world data study are comparable with clinical trials. Despite frequent use of cisplatin-based 1L tx and vinflu- nine 2L tx, per recent guidelines, outcomes are generally still poor.

Legal entity responsible for the study: F. Hoffmann-La Roche Ltd.
**Background:** Health related quality of life (HRQoL) data and utilities derived from preference-based scales are needed for pharmacoeconomic studies. However, available data for hospitalized Medical Oncology patients are scarce or restricted to specific neoplasms. The aim of this work was to obtain health state utilities (HSU) from a heterogeneous population of cancer inpatients admitted to a Medical Oncology department. Methods: Between Dec-15 and March-16, we prospectively collected HRQoL data from consecutive patients admitted to a Medical Oncology ward using EuroQoL 5-dimensions 5-levels instrument (EQ-5D-5L) and EQ-5D-5L visual analogic scale (VAS). Utility weights were assigned according to Spain social tariff using EuroQol crosswalk value sets. Non-parametric tests (Mann Whitney U, Kruskal-Wallis) were used to evaluate differences of HSU between groups. Results: 215 patients were included; median age: 62 (16-88); ECOG: 1 (45%), 2 (43%), 3-4 (12%); site: lung (27%), breast (15%), colorectal (15%), urogenital (13%); stage: I-II (11%), III (15%), IV (74%); active anticancer treatment: 87%; death during admission: 17% (8%); Mean (SD) EQ-5D-5L HSU for all patients was 0.52 (0.41); VAS: 52 (2). Mean (SD) values for EQ-5D-5L domains: mobility, 2.21 (1.24); self-care, 2.23 (1.49); usual activities, 2.89 (1.41); pain/discomfort, 1.94 (1.29); anxiety/depression: 2.12 (0.94). Differences between groups are shown in Table. Conclusions: Average utility (EQ-5D-5L) for Medical Oncology inpatients is 0.52; lowest scores in this population were obtained for pain/discomfort and anxiety/depression domains. Significant differences were observed between different EQCOG levels, tumor stages, admission causes and type of treatment.

Legal entity responsible for the study: Francisco Ayala de la Peña

Funding: None

Disclosure: All authors have declared no conflicts of interest.

### 1118P Health related quality of life and utility weights of medical oncology patients

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**Background:** Health related quality of life (HRQoL) data and utilities derived from preference-based scales are needed for pharmacoeconomic studies. However, available data for hospitalized Medical Oncology patients are scarce or restricted to specific neoplasms. The aim of this work was to obtain health state utilities (HSU) from a heterogeneous population of cancer inpatients admitted to a Medical Oncology department. Methods: Between Dec-15 and March-16, we prospectively collected HRQoL data from consecutive patients admitted to a Medical Oncology ward using EuroQoL 5-dimensions 5-levels instrument (EQ-5D-5L) and EQ-5D-5L visual analogic scale (VAS). Utility weights were assigned according to Spain social tariff using EuroQol crosswalk value sets. Non-parametric tests (Mann Whitney U, Kruskal-Wallis) were used to evaluate differences of HSU between groups. Results: 215 patients were included; median age: 62 (16-88); ECOG: 1 (45%), 2 (43%), 3-4 (12%); site: lung (27%), breast (15%), colorectal (15%), urogenital (13%); stage: I-II (11%), III (15%), IV (74%); active anticancer treatment: 87%; death during admission: 17% (8%); Mean (SD) EQ-5D-5L HSU for all patients was 0.52 (0.41); VAS: 52 (2). Mean (SD) values for EQ-5D-5L domains: mobility, 2.21 (1.24); self-care, 2.23 (1.49); usual activities, 2.89 (1.41); pain/discomfort, 1.94 (1.29); anxiety/depression: 2.12 (0.94). Differences between groups are shown in Table. Conclusions: Average utility (EQ-5D-5L) for Medical Oncology inpatients is 0.52; lowest scores in this population were obtained for pain/discomfort and anxiety/depression domains. Significant differences were observed between different EQCOG levels, tumor stages, admission causes and type of treatment.

Legal entity responsible for the study: Francisco Ayala de la Peña

Funding: None

Disclosure: All authors have declared no conflicts of interest.

### 1119P A trial-based EUROQOL EQ-5D health utility analysis in patients with classical Hodgkin's lymphoma

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**Background:** Pembrolizumab has shown a high response in patients with classic Hodgkin lymphoma (cHL). This trial aimed to analyze disease progression after pembrolizumab vedotin in KEYNOTE (KN)-087 and the results has been presented. This study aimed to evaluate the health-related quality of life (HRQoL) of the trial patients in KN087. Methods: KN-087 is an ongoing single-arm multi-center, non-randomized Phase II trial evaluating pembrolizumab 200mg Q3W IV in patients with relapsed or refractory cHL. In KN-087, HRQoL data were collected at baseline and every drug administration over the 18 months of follow-up. HRQoL was assessed using both the EQ-5D and EORTC QLQ-C30 instruments. The generic health status assessments from both instruments were converted to population-based utility values using published algorithms. More specifically, US-based scoring was applied to US patients, UK-based scoring for UK patients and EU-based scoring for all other patients. HRQoL was reported by status of respond and disease progression. Response was defined based upon IWG criteria. Furthermore, stratified analyses were conducted to examine the health disabilities of the patients who experienced grade 3+ adverse events (AEs), and by ECOG performance and the number of prior therapies.

**Results:** Among 210 trial patients, HRQoL data were collected for 205 patients at baseline and the mean health utility score was 0.795 (95% CI 0.738-0.788). Mean health utility score among responders and non-responders was 0.826 (95% CI 0.811-0.842) and 0.760 (95% CI 0.718-0.801), respectively. The difference is considered clinically significant. Mean utility decreased from 0.820 (95% CI 0.807-0.833) for time spent prior to progression to 0.806 (95% CI 0.780-0.832) post disease progression. Progression-free patients who experienced grade 3+ AEs (N = 17) had a mean health utility of 0.736 (95% CI 0.662-0.811), compared with 0.825 (95% CI 0.811-0.838) among those did not.

**Conclusions:** The results showed a substantial HRQoL impact of RCR cHL. Treatment response was associated with significant clinically meaningful improvement in HRQoL. The utility estimates from the study are important for economic evaluations of treatments in RCR cHL patients.

Clinical trial identification: NCT02453594

Legal entity responsible for the study: Merck

Funding: Merck

Disclosure: E. Wu, J. Liao, A. Balakumaran: Employee of Merck & Co Inc.

### 1120P Real world comparison of common patient reported symptoms with health utility scores in cancer outpatients

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**Background:** Health utility scores (HUS), a form of health-related quality of life (HRQoL) assessments useful in economic analyses, as such the EuroQol (EQ-5D) were originally standardized to health state preferences in healthy individuals. To demonstrate clinical appropriateness in cancer patients, we assessed the association of common cancer symptoms with EQ-5D HUS. Methods: Adult cancer outpatients were surveyed cross-sectionally using the Edmonton Symptom Assessment System (ESAS), the EQ-5D-5L, and clinicodemographic variables. ESAS rated symptoms from 0-10. HUS were derived from the EuroQol (EQ-5D) were originally standardized to health state preferences in healthy individuals. To demonstrate clinical appropriateness in cancer patients, we assessed the association of common cancer symptoms with EQ-5D HUS. Results: 3784 patients across multiple cancers, 27% were palliative at assessment. There were significant correlations between each ESAS symptom score and HUS (p < 0.001 for each comparison; Spearman coefficients: 0.20 to 0.42); the highest were for pain (R = 0.42), fatigue (R = 0.39), and depression (R = 0.35). In multivariable analyses, pain and depression symptom scores remained highly associated with HUS (p < 0.001 each), while fatigue was of borderline significance (p = 0.059). Despite correlation, prediction of HUS by global ESAS scores was poor, with the highest prediction ability at 0.25. Because ESAS and EQ5D shared common symptom questions (pain, depression/anxiety), we evaluated if we could map and replace those EQ5D questions with ESAS. Spearman correlation of pain symptoms by EQ5D and ESAS was 0.91, while for depression/anxiety, 0.90. Replacing both questions yielded a correlation of 0.83.

**Conclusions:** HUS is associated with many cancer symptoms, including pain, fatigue, nausea, depression, anxiety, dyspnoea, loss of appetite, and shortness of breath. EQ-5D-3L derived HUS have clinical utility. On exploratory analysis, we cannot replace...
accurately the EQ5D with ESAS, although we can replace two symptom questions within EQ5D with ESAS with high correlation.

Legal entity responsible for the study: Princess Margaret Cancer Centre, UHN, Toronto, Canada

Funding: Cancer Care Ontario

Disclosure: All authors have declared no conflicts of interest.

1121P

Costs of dacomitinib versus placebo in pretreated unselected patients (pts) with advanced NSCLC: CCTG BR.26


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Background: Dacomitinib, a potent irreversible pan-HR kinase inhibitor, has activity in EGFR mutant (mt) lung cancer. BR.26, completed in 2013, compared dacomitinib versus placebo in unselected pts who had received both chemotherapy (1 or 2 lines) and a first-generation EGFR TKI for advanced NSCLC. Dacomitinib pts had significantly improved tumour response rate, PFS, and time to symptom deterioration but not improved survival (OS). A trend towards improved OS was seen in pts with KRAS wildtype (wt) tumours (KRAS unknown in 42%). A prospective economic evaluation was planned for Canadian and Australian pts.

Methods: Resource utilization and utility scores (EQ-5D-5L) were collected prospectively in 385 trial participants from Canada and Australia. Direct medical costs were applied to resources in 2015 Canadian dollars (CAD) from the Canadian public health care payer perspective. Dacomitinib is not approved for marketing, thus we used a utility score of 0.95 and applied to costs in 2015 Canadian dollars.

Results: Incremental outcomes and costs by treatment arm are shown below. Mean utility scores were similar, although higher in dacomitinib-treated pts with KRAS wt or EGFR mt.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Survival (ΔE, years)</th>
<th>Quality-adjusted survival (ΔE, QALY)</th>
<th>Cost (ΔE, 2015 CAD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.0014</td>
<td>0.011</td>
<td>$524 $3,944 $7,365</td>
</tr>
<tr>
<td>Dacomitinib</td>
<td>0.0104</td>
<td>0.069</td>
<td>$1,829 $5,489 $9,149</td>
</tr>
</tbody>
</table>

Conclusion: Dacomitinib is not approved for marketing and we used a utility score of 0.95 and applied to costs in 2015 Canadian dollars.

Legal entity responsible for the study: Canadian Clinical Trials Group (CCTG)

Funding: Pfizer

Disclosure: P. Bradbury: Honorarium from Pfizer and Merck. P. Ellis: In the past two years, received honoraria for talks from Boehringer Ingelheim and Novartis. G. Liu: Honoraria from AstraZeneca, Pfizer, Novartis and Takeda. R. Sangha: Honoraria from Pfizer, Boehringer Ingelheim, AstraZeneca, Roche, Eli-Lilly, Bristol-Myers Squibb and Merck. M. Boyer: I’ve received Honoraria (paid to my institution) from Pfizer, Boehringer Ingelheim and Astra Zeneca. G. Goss: Honoraria from Pfizer, AstraZeneca, Boehringer Ingelheim, Lilly, Bristol-Myers Squibb, and Celgene. L. Seymour: Pfizer provided funding for the BR.26 trial. N.R. Leigh: Research funding (institution) - Novartis Unrelated CME (not speaker’s bureau) - travel/honouraria - AstraZeneca, Merck Sharpe & Dohme, Pfizer, Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

1122P

Feasibility of routine collection of health state utilities using EQ-5D in a breast cancer outpatient clinic

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Background: Routine collection of health state utilities in the clinical setting may produce data more representative of the real-world population for use in cost-utility models and guide decision making. We are currently carrying out a cross-sectional study to assess the feasibility of routine administration of EQ-5D to breast cancer patients in a multidisciplinary oncology clinic, in an academic cancer centre in Ontario, Canada.

Methods: English literate women undergoing treatment or on follow-up for their breast cancer (stage I to IV), are being recruited during their scheduled visit to the cancer centre, preferably after completing the implemented routine symptom screening using the Edmonton Symptom Assessment System (ESAS). Consenting patients complete EQ-5D-5L in tablets, followed by a socio-demographic questionnaire and feedback questions pertaining to study conduct. Answers are stored in a research database and linked to diagnostic and treatment data. Feasibility will be assessed primarily by the proportion of patients who fully complete EQ-5D and by their willingness to complete the instrument at each clinic visit.

Results: To date, 474 women were approached; 262 (59%) were eligible and consented to participate (target enrolment: 341). Median age of participants was 56 years (range: 28-90); 24% had metastatic disease. All participants were English literate, but 59% were born outside Canada and speak primarily other languages at home. Ninety-eight percent of recruited patients completed EQ-5D at each visit, compared with 84% who completed ESAS on the same day (63% completed ESAS voluntarily prior to enrolment; 21% agreed on completing ESAS for study purposes only). Median time for EQ-5D completion was 84 seconds. Most patients (82%) had no problems using the tablet. Willingness to continue to complete EQ-5D at each clinic visit was not affected by disease status (stage I to III versus stage IV) and 74% would definitely/very likely continue to answer EQ-5D regularly at each clinic visit.

Conclusions: These preliminary results indicate that routine collection of EQ-5D in clinical practice might be feasible, although the completion rate might be overestimated by the cross-sectional design of the study.

Legal entity responsible for the study: Sofia Torres

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1123P

The cost of expensive breast cancer drugs

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Background: Increasing healthcare costs are a major challenge in medical oncology, since the total costs of oncology can account for up to 30% of the total hospital expenditures. As many novel (expensive) cancer treatments are being developed, it is important to be transparent about drug prices from an early research stage on. To assess the potential financial impact of pipeline drugs, their expected future prices can be deducted from prices of currently used drugs. As an overview of the standard prices of expensive breast cancer treatments in European countries is lacking, this review aimed to synthesise all evidence on costs of approved, expensive breast cancer drugs in the Netherlands.

Table: 1121P

<table>
<thead>
<tr>
<th>Incremental mean outcome with dacomitinib over placebo</th>
<th>All patients (n = 385)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS wild type (KRAS known n = 165)</td>
<td>EGF (EGFR known n = 80)</td>
</tr>
<tr>
<td>Survival (ΔE, years)</td>
<td>0.0014</td>
</tr>
<tr>
<td>Quality-adjusted survival (ΔE, QALY)</td>
<td>0.011</td>
</tr>
<tr>
<td>Cost (ΔE, 2015 CAD)</td>
<td>$524 $3,944 $7,365</td>
</tr>
</tbody>
</table>

| Pd group | $10,783 | $12,809 | $199 $4,083 $7,968 $11,853 |

Annals of Oncology
Methods: A literature review was performed to create an overview of all approved, expensive drugs in the Netherlands. Standard drug costs were retrieved via the Dutch administrative health authority (ZINL). Drugs were considered expensive if the standard price of the drug was more than €10 per unit or if the cost of a treatment with that particular drug exceeded €1000 on average per patient.

Results: In the Netherlands 25 breast cancer drugs are approved with a standard price of more than €10 per unit. After excluding drugs with expected treatment costs less than €1000, 19 drugs were included in the analysis. The standard drug price is €7,943 on average (range 663–845,452), and the average number of cycles per patient is 10.5 (range 4–25.3 cycles). This results in average treatment costs per patient of expensive drugs of €17,968 (range 9,103–877,123). Four drugs that initially ranked low based on standard drug unit prices (rank 10–19), rank substantially higher (rank 1–10) when ranking total treatment costs.

Conclusions: Ranking standard drug prices per unit may not be very informative. It would be valuable to rank drug treatment costs, based on treatment length and dosage estimates. However, in the Netherlands the expected treatment length for a particular drug is not straightforwardly reported in official approval reports. Furthermore, actual prices of expensive drugs may differ from standard drug prices, by which treatment costs might be deviant. Extending standardization of reporting and calculation of drug treatment costs would be valuable and particularly relevant when extending this type of cost calculations to other countries.

Legal entity responsible for the study: University of Twente - Health Technology and Services Research

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1125P

The cost-effectiveness of EndoPredict to inform adjuvant chemotherapy decisions in early breast cancer

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Background: Chemotherapy alongside endocrine treatment in ER+ breast cancer patients post-resection of a primary tumour has been estimated to reduce mortality rates by up to 30%. However, the high cost of the therapies, heterogeneous nature of the disease and adverse event profile implies that not all patients should receive the treatment. Many existing prognostic tools such as the NPI, PREDICT, and Adjuvant! Online may not definitively predict the risk profile of patients, resulting in an indeterminate risk classification. In such cases gene expression profiling tests such as EndoPredict can aid the treatment decision. It is important to examine if the test represents a cost-effective use of limited NHS resources in such intermediate risk patients.

Methods: This small (n = 151) multi-centre, two-stage study evaluated the cost-effectiveness of EndoPredict in patients with no clear treatment based on current prognostic criteria. The primary analysis examined whether EndoPredict test results increased or decreased the use and intensity of chemotherapy and the associated direct cost implications. Secondly, a mathematical model was constructed to determine how the change in treatment decisions impacted the long term health of the population, and the future implications to the NHS.

Results: A cost increase per patient treated with chemotherapy was identified when EndoPredict test results were available (€149), alongside no significant change in the total number being prescribed chemotherapy. However, chemotherapy was offered to a very different patient population, with 36.9% of patients having a change in treatment decision. The long term analysis found the use of EndoPredict to be associated with greater total costs but a potential increase in population health, resulting in an incremental cost-effectiveness ratio of €26,836 per quality adjusted life year.

Conclusions: While EndoPredict was found to be more expensive overall, the ability of the EPClin score to affect a more optimal allocation of chemotherapy, resulted in long term health gains. This result was on the margin of what is conventionally considered a cost-effective use of limited NHS resources and subject to significant uncertainty.

Clinical trial identification: ISRCTN69922010

Legal entity responsible for the study: Sussex Health Outcomes Research and Education in Cancer

Funding: Myriad

Disclosure: S. Hinde C. Theriou, S. May, L. Matthews, A. Arbon, L. Fallowfield, D. Bloomfield: This research was funded through an unrestricted educational grant from Myriad.

1126P

The evolution of value with filgrastim in oncology

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Background: The value of drugs will evolve over time as new evidence for risks and benefits emerge and the price of a drug changes.

Methods: A NICE Evidence Search on March 1, 2017 revealed 25 systematic reviews and 55 economic evaluations of filgrastim.1

Results: Initial Health Technology Assessments (HTA) suggested low value due to high drug cost and no evidence for significant gain in Overall Survival (OS). More recent meta-analyses of placebo-controlled randomized trial data show absolute OS gains of 3.2% (95% CI 2.1—4.2%) from filgrastim support of cytotoxic chemotherapy2 and falling costs due to biosimilar competition.


Legal entity responsible for the study: N/A

Funding: None

Table: 1129P Costs Incurred During the Treatment Exposure Window for 1L and 2L mBC Therapies

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treatment Group</th>
<th>1L</th>
<th>2L</th>
<th>1L</th>
<th>2L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>Sample size, n (%)</td>
<td>411 (100%)</td>
<td>189 (100%)</td>
<td>162 (39.4%)</td>
<td>22 (11.6%)</td>
</tr>
<tr>
<td></td>
<td>Total cost per patient, mean (SD)</td>
<td>$36,793 ($28,754)</td>
<td>$26,732 ($21,143)</td>
<td>$35,570 ($25,770)</td>
<td>$25,267 ($16,494)</td>
</tr>
<tr>
<td></td>
<td>mBC-related cost per patient, mean (SD)</td>
<td>$18,246 ($16,655)</td>
<td>$12,939 ($13,340)</td>
<td>$19,116 ($16,660)</td>
<td>$13,529 ($11,872)</td>
</tr>
<tr>
<td></td>
<td>AE-related cost per patient, mean (SD)</td>
<td>$7,629 ($12,399)</td>
<td>$4,988 ($9,471)</td>
<td>$6,240 ($10,814)</td>
<td>$4,170 ($6,473)</td>
</tr>
<tr>
<td></td>
<td>Other costs per patient, mean (SD)</td>
<td>$12,990 ($16,906)</td>
<td>$10,363 ($14,753)</td>
<td>$11,900 ($15,817)</td>
<td>$7,892 ($6,823)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Overall</th>
<th>185 (45.0%)</th>
<th>71 (37.6%)</th>
<th>64 (15.6%)</th>
<th>95 (50.8%)</th>
</tr>
</thead>
</table>
| SeeER-Medicare linked data. Annual survival rates were calculated for treated and untreated pts. Total costs were estimated during the treatment exposure window for HC visits and treatment for mBC-related, AE-related, and other costs; all costs were converted to 2016 US dollars. Results: Overall, 411 eligible pts received 1L therapy and 189 (46.0%) subsequently received 2L therapy. For all 1L treated pts, the 1, 2, and 3-year survival rates from mBC diagnosis were 56.3%, 25.6%, and 13.5%, compared to 12.9%, 6.0%, and 4.7% for untreated pts (n = 804). For 2L pts, the 1, 2, and 3-year survival rates from 2L treatment initiation were 32.8%, 14.9%, and 7.7%. For all regimens, the highest per-patient cost occurred in the outpatient setting, followed closely by emergency, then inpatient, SNF, and lastly by hospice. Conclusions: In general, mBC pts had poor survival outcomes, particularly for untreated pts. Less than half of mBC pts received guideline-endorsed 1L cis-combo therapy. mBC-related outpatient and emergency HC utilization were primary drivers of the per-patient economic burden. During the treatment exposure window, total costs were considerable across treatment regimens, with the average total cost during 1L and 2L treatment exceeding sixty thousand dollars per patient. Legal entity responsible for the study: Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA provided funding for this study, yet the authors take full responsibility for the work as a whole, including the study design, access to data reported in the manuscript, and the decision to submit and publish the manuscript. All authors approved the final manuscript to be published. Funding: Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA. Disclosure: K. Flannery, X. Cao, J. He, Y. Zhong, Employee of Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA. A. Kamat: Research funding: FKD Industries; Photocure; Merck; and Heat Biologics. Consulting or advisory role: Cepheid; Photocure; Telesta Therapeutics; Sanofi; Merck; Astra; Novartis; Theraslase; Heat Biologics; Spectrum Pharmaceuticals; and Oncogenx. All other authors have declared no conflicts of interest.

1130P Investigating discrepancies in assessments of PFS by study investigators and independent review

C.F. Jones, J.F. Soto Barrientos, G. Mannickendam

Oncology, PRMA Consulting, Fleet, UK

Background: OS is considered the gold standard trial endpoint, particularly for health technology assessment. However OS faces challenges – from subsequent therapy bias to needing long trials that delay patients’ access to promising medicines. PFS is often used either instead of, or alongside – OS – by regulators, clinicians, payers, and more recently, value frameworks in oncology. PFS is without a standardized measure. We examine the extent of differences between independent central review (ICR) and investigator assessed (INV) PFS. We aim to increase understanding of potential variability in PFS measurement, relevant associations and possible causal factors to inform appropriate use of PFS in payer and clinician decision-making.

Methods: We searched ClinicalTrials.gov for ‘progression free survival’ and ‘cancer’, filtering for interventional phase 2 or 3 studies with results. Studies were extracted and the primary and secondary outcomes filtered for ICR and INV based PFS. We searched PubMed with the same criteria; full articles were reviewed and studies reporting for ICR and INV based PFS included. For comparative trials, we calculated difference in median PFS between intervention and control arms for ICR and INV based PFS. For single arm trials, the difference between ICR and INV based PFS was calculated where both were reported.

Results: Of 365 studies from clinical trials.gov: 48 reported ICR based PFS and 45 reported INV. 6 studies reporting both were included. Of 49 studies from PubMed; 21 were included. There was 1 duplicate. The majority of studies were comparative (23/26), in solid tumors (21/26), and published in the last 5 years (21/26). Calculating the PFS gain at the median, the difference between the ICR based gain and the INV based gain ranged from 0.1 to 4.3 months. In 9 comparisons the gain with ICR
was greater than the gain with INV. In 6 comparisons the difference in PFS gain was ≥2 months, a difference of up to 54% of the gains alone.

Conclusions: ICR and INV based PFS produce different estimates of PFS gain in clinical trials, but it remains uncommon for studies to report both ICR and INV based PFS. Both measures should be required, to improve consistency of comparison across trials and transfer of trial results to real world practices and decision-making.

Legal entity responsible for the study: PRMA Consulting Ltd

Funding: PRMA Consulting


### Table: 1131P Cumulative per-patient costs from 3 months before diagnosis to end of follow-up (% total)

<table>
<thead>
<tr>
<th>Cost category</th>
<th>All patients (N = 1,873)</th>
<th>No chemotherapy (N = 1,035)</th>
<th>1L only (N = 310)</th>
<th>2L only (N = 204)</th>
<th>3L + (N = 124)</th>
<th>P-value (3L+ vs 2L)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median follow-up time, months</strong></td>
<td>7.5</td>
<td>3.8</td>
<td>11.8</td>
<td>16.1</td>
<td>26.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean costs (%, $US)</td>
<td>82,912 (100)</td>
<td>57,208 (100)</td>
<td>99,422 (100)</td>
<td>123,262 (100)</td>
<td>162,549 (100)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inpatient</td>
<td>43,990 (53)</td>
<td>36,840 (64)</td>
<td>51,358 (52)</td>
<td>54,698 (44)</td>
<td>55,575 (34)</td>
<td>0.359</td>
</tr>
<tr>
<td>Physician (incl. chemo for treated pts)</td>
<td>21,426 (26)</td>
<td>10,087 (18)</td>
<td>26,735 (27)</td>
<td>39,955 (32)</td>
<td>63,476 (39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Outpatient (incl. chemo for treated pts)</td>
<td>9,189 (11)</td>
<td>3,367 (6)</td>
<td>12,199 (12)</td>
<td>18,626 (15)</td>
<td>29,742 (18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Home health</td>
<td>2,631 (3)</td>
<td>2,042 (4)</td>
<td>3,256 (3)</td>
<td>3,018 (2)</td>
<td>4,329 (3)</td>
<td>0.166</td>
</tr>
<tr>
<td>Hospice</td>
<td>3,208 (6)</td>
<td>3,624 (6)</td>
<td>2,337 (2)</td>
<td>2,671 (2)</td>
<td>4,211 (3)</td>
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</tr>
<tr>
<td>Durable medical equipment</td>
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<td>550 (1)</td>
<td>1,771 (2)</td>
<td>1,627 (1)</td>
<td>2,503 (1)</td>
<td>0.849</td>
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<tr>
<td>Prescription drugs (not incl. chemo)</td>
<td>1,351 (2)</td>
<td>698 (1)</td>
<td>1,767 (2)</td>
<td>2,668 (2)</td>
<td>2,912 (2)</td>
<td>0.652</td>
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</table>

*Physician costs are non-institutional claims largely from physicians who bill for services provided in the office

BOutpatient costs are claims from institutional outpatient providers
Background: Parallel to advances in cancer therapeutics in the clinics, high-quality and patient-centred management of cancer or treatment-related complications during non-elective attendance especially to a non-specialist hospital is crucial in achieving excellent patient outcome. AOS was innovated in the UK to meet this need and has rapidly expanded in recent years. Here, we describe findings of an on-going audit of this expanding networked service within Greater Manchester and Cheshire East County consisting of 10 district general hospitals in collaboration with a regional specialist cancer centre (The Christie NHS Foundation Trust).

Methods: Information related to any hospital episodes warranting AOS input was collated from all participating hospitals using standardised proforma and analysed.

Results: Between Jan 2015 - Sep 2016, 7638 non-elective hospital attendances were recorded of which 58% occurred within working hours. Common cancer sites were lung 16%, breast 15%, lower GI 12%, urology 12%, upper GI and HPB 9%, haematology 7%, gynaecology 6%, cancer of unknown primary (CUP) 6%, and others 7%. Majority were related to cancer complication 40% (Type III), treatment - related 32% (Type II), new cancer diagnosis 10% (Type I) and others 17%. 94% of AOS involvement occurred within 24hr of attendance. Level of intervention by AOS was considered major in 60% while 30% and <10% was intermediate or minor respectively. Median length of stay (LOS) is 4 days, 20% of episodes lasted <24hr (11.2% admission avoidance), 50% 1-7 days, and 30% 2-6 weeks (predominantly type I and III).

Conclusions: This large multi-sites audit documented the service delivery pattern of a cancer centre (The Christie NHS Foundation Trust).

Additional information: The research was funded by the Christie NHS Foundation Trust.

Disclosure: All authors have declared no conflicts of interest.

Funding: None
Phase III randomized controlled trial of adjuvant chemotherapy in patients with resected primary lung cancer

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Results:
(0.235 were 70.0% and 57% in group A and 64.7% and 45.1% in group B, respectively. The hazard ratio (HR) was 0.451 (0.235–0.807) by multivariate analysis. The 2- and 5-year overall survival rates were 70.0% and 57.9% in group A and 64.7% and 51.4% in group B, respectively. P values of Log-rank test between groups were 0.0059. Subgroup analysis for the OS between the two groups revealed no significant differences in patients receiving immunotherapy.

Conclusions:
Non-small-cell lung cancer patients benefited from adoptive cellular immunotherapy as an adjuvant to surgery. Immunological analysis of cell surface markers in regional lymph nodes of subjects receiving chemotherapy indicated that the CD8+/CD4+ T-cell ratio was elevated in survivors.

Clinical trial identification:
The University Hospital Medical Information Network in Japan (UMIN: 000007525).

Legal entity responsible for the study:
Chiba Cancer Center, Japan

Funding:
None

Disclosure:
All authors have declared no conflicts of interest.

Phase 1b/2 Study (SCORES) assessing safety, tolerability, and preliminary anti-tumor activity of durvalumab plus AZD9150 or AZD5690 in patients with advanced solid malignancies and squamous cell carcinoma of the head and neck (SCCHN)


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Background:
Anti-tumor activity of durvalumab (D), a programmed death ligand (PDL1) blocking antibody, may be enhanced by overcoming intratumoral immune suppression. The selective Generation 2.5 antisense oligonucleotide STAT3 inhibitor AZD9150 (STATi), a small molecule CXCL2 inhibitor AZD5690 (CX2i), and CTLA4 inhibitor tremelimunab (T) are in evaluation.

Methods:
Part A, dose escalation in solid tumors, evaluated STATi+ (D or D±T) and CX2i+ (D or D±T) for safety, pharmacokinetics, pharmacodynamics and maximum tolerated dose. Part B, dose expansion in SCCHN, tested STATi+ (3 mg/kg) + D and CX2i+ (40 mg BID) + D in PDL1 pre pared naïve pts and as monotherapy for Objective Response Rate (ORR) and Disease Control Rate (DCR).

Results:
Part A showed STATi+ and CX2i+ as safe and tolerable combinations with confirmed partial responses (cPR) in multiple tumor types and 2 confirmed complete responses (cCR) in breast and prostate cancer (>4 weeks [wks] on treatment). STATi+DT had a cPR in sarcoma at 12 wks. In Part B (STATi+D reported here), the PDL1 naïve arm had 25% ORR (4 cPR, 1 unconfirmed PR [uPR]), 3 Human Papilloma Virus (HPV) negative and 2 unknown), 45% DCR (9/20) was observed at 12 wks, and 39% of pts (6/20) remain on treatment at 25 wks. One cPR pt is unconfirmed CR at data cut off. In the PDL1 pretreated arm, 1 pt had complete metabolic response and 1 pt had uPR. Safety and tolerability were confirmed for STATi+D in SCCHN pts, with manageable and reversible adverse events of thrombocytopenia and liver enzyme increases for each, (Grade 3/4 in 3.4% of pts dosed). 2 STATi+D related discontinuations occurred.

Conclusions: Initial ORR and DCR data suggest enhanced antitumor activity results from combining a PDL1 antagonist (D) with an agent targeting immunosuppression in the tumor microenvironment (STATi) compared to PDL1 monotherapy. The combination may prove to provide a tolerable and effective option for patients with recurrent/metastatic SCCHN in the naive and PDL1 pre treated setting and other solid tumor types being studied.

Clinical trial identification:
NCT02499928

Legal entity responsible for the study:
AstraZeneca PLC

Funding:
AstraZeneca

Disclosure:
E.E. Cohen: Contributed to AstraZeneca, Bristol-Myers Squibb, Human Longevity, Merck, Merck Serrano, and Pfizer. Received expenses for travel or accommodation from AstraZeneca, Merck, and Pfizer. Holds stock in Human Longevity, Inc. D.S. Hong: Receives grants from Bayer, Lilly, Genentech, LOXO, Pfizer, Amgen, Mirati, Ignyta, Merck, Daichi-Sankyo, and Eisai. Travel expenses were provided by MiRNA and LOXO. Contributed to Bayer, Baxter, and Guidespit Global. He founded Oncopreceptor. T. Wise Draper: Received funding for investigator-initiated studies from Bristol-Myers Squibb and Merck. D. Schrijvers: Participated in studies sponsored by Cougar, Janssen, and Bayer. Served on the advisory board of Janssen and Bayer Belgium. Spoken at events organized by Janssen and Bayer Belgium. R. Messia Nin: Served an advisory role for AstraZeneca, Merck SL, Bayer, and Bristol. Received conference honoraria from Bristol and Merck SL, M.L. Scott, P. Lyne, P. McCoon, C.E. Cook: Employee of, and owns stock in, AstraZeneca. G. Mugurum: Employee of AstraZeneca and owns stock in AstraZeneca and Pfizer. M.M. Mehra: Employed by AstraZeneca. U. Khiladi: Receives speaker honoraria, and served on advisory boards, for AstraZeneca, Merck, MSD, Pfizer, Novartis, and Innate. Participates in research sponsored by AstraZeneca and Merck. All other authors have declared no conflicts of interest.

Nivolumab and ISA 101 HPV vaccine in incurable HPV-16+ cancer


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Background:
Vacccines directed against Human Papilloma Virus (HPV) do not generally mediate regression of invasive cancer. To test the hypothesis that the efficacy of vaccine-induced T cells may be amplified through treatment with immune checkpoint antibodies, we conducted a phase II trial of ISA 101, a synthetic long-peptide HPV-16 vaccine, and nivolumab in pts with incurable HPV-16+ cancer.

Methods:
Tumors were HPV-genotype 16 by Cervista HPV16/18. Patients were ECOCOG PS 0-1 with up to one prior regimen for recurrence. ISA101 100 mcg/peptide was given Days 1, 22, 50. Nivolumab 3 mg/kg was given in every 2 week beginning day 8 for up to one year. Imaging was obtained baseline, 11 wks and every 6 wks thereafter. The primary objective was assessment of overall response rate (ORR) targeting 30% Secondary objectives: tolerability, PFS. A Simon two stage design required response in 21/25 first stage and 5/25 second stage.

Results:
The trial accrued 24 patients; 22 with oropharynx cancer (OPC) and 1 pt each with anal and cervical cancer. 18 pts (75%) had progression within 6 mos of prior platin and 1 was platinum naïve. 12 pts (50%) had prior cetuximab. Treatment was frontline for recurrence in 10/24 and second line in 14/24. ORR is 33% (8/24): 1 CR, 7 PR (1 unconfirmed), 3(13%) SD, 13 (54%) PD. ORR in OPC pts is 36% (8/22): 6/8 pts with PR progressed within 6 mos of prior platin. Median duration of response 50.1 + wks (6.4+ wks): 5/8 pts with PR remain in response. Median PFS is 2.7 mos [95% CI 2.5±8.0 mos] and median OS is not reached with median follow up time among censored pts 8.6 mos. PFS rate at 6 mos. 39% (16-52%) OS rate at 6 mos 74%, (51-87%). Toxicity:

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grade 3 transaminase and grade 4 lipase elevation in 1 pt each, grade 1-2 toxicity: fever (3 pts), injection site reaction (6 pts), transaminase elevation, fatigue, nausea (3 pts each).

Conclusions: The primary endpoint was met and ORR of 36% in OPC pts compares favorably to 16% for nivolumab monotherapy in p16-OPC pts in CheckMate 214 (Ferris RL et al in Eng J Med 2016; 375:1856). These data suggest that the efficacy of vaccine-induced T cells can be augmented by anti-PD-1 therapy, mitigating the influence of an immunosuppressive microenvironment. Our findings merit confirmation in a larger randomized trial. Correlation of efficacy outcomes with immunoprofiling of tumors will be presented.

Clinical trial identification: NCT02428892
Legal entity responsible for the study: UT MD Anderson Cancer Center
Funding: UT MD Anderson Cancer Center

Disclosure: S. van der Burgh, C. Mielé: Employed by ISA Pharmaceuticals Inc. All other authors have declared no conflicts of interest.

Interim analysis of the phase 3 ADAPT trial evaluating rocapuldencel-T (AGS-003), an individualized immunotherapy for the treatment of newly-diagnosed patients with metastatic renal cell carcinoma (mRCC) 4

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1Division of Hematology Oncology, Cedars-Sinai Medical Center, Los Angeles, CA, USA, 2Research and Development, Argos Therapeutics, Durham, NC, USA, 3GU Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA, 4Medical Oncology, University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA, USA, 5Surgical Oncology, Far Chase Cancer Center, Philadelphia, PA, USA, 6Department of Urology, Emory University, Atlanta, GA, USA, 7Urology, Spectrum Health Cancer Center, Grand Rapids, MI, USA, 8Urology, UT MD Anderson Cancer Center, Houston, TX, USA

Background: Rocapuldencel-T is an investigational immunotherapy formulated with RNA isolated from the patient’s tumor to program autologous dendritic cells with tumor-specific antigens. It is administered chronically via intradermal injection to activate a tumor-specific memory T-cell response.

Methods: The Phase 3 ADAPT trial was designed to evaluate overall survival (OS) of rocapuldencel-T in combination (Combe) with standard-of-care (SOC) for the treatment of newly diagnosed mRCC as compared to SOC alone (Control). It included 462 patients were randomized 2:1 from February 2013 - October 2015. In sites across North America, Europe and Israel.

Results: 462 patients were randomized 2:1 from February 2013 - October 2015. In February 2017, an interim analysis by the Independent Data Monitoring Committee 462 patients were randomized 2:1 from February 2013 - October 2015. In

Conclusion:

Clinically, the interim analysis of the phase 3 ADAPT trial evaluating rocapuldencel-T (AGS-003), an individualized immunotherapy for the treatment of newly-diagnosed patients with metastatic renal cell carcinoma (mRCC)

11370

Immunopeptide-based predictive biomarkers for PD-L1 expression in urothelial cancer patients

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Background: High level expression of PD-L1 in urothelial tumors has been shown to predict response to anti-PD-L1 therapy. Immune-related Adverse Events (irAEs) are common with anti-PD-L1 therapy, especially transient lymphopenia. Numerous studies have demonstrated that inter-cellular expression of PD-L1 is a potential therapeutic target. The role of PD-L1 expression in predicting clinical response to anti-PD-L1 therapy remains to be determined.

Methods: PD-L1 expression was evaluated with standard IHC methods using the Ventana platform and an approved antibody, clone SP263. Clinical trial data from the Phase III KEYNOTE-045 trial, a non-randomized, controlled trial of pembrolizumab versus chemotherapy in patients with advanced urothelial carcinoma, was used to assess the ability of PD-L1 IHC to predict the clinical benefit of pembrolizumab. The entire set of 368 patients was used as the training set. The primary endpoints were OS and ORR. A retrospective analysis was performed to correlate the PD-L1 expression status with the clinical outcomes. The enrolled patients were selected based on the PD-L1 IHC expression status cut-off, 5%.

Results: The number of patients with PD-L1 IHC expression ≥5% and <5% were 146 and 222, respectively. PD-L1 ≥5% was associated with higher ORR (28% vs. 7%) (P=0.001) and longer OS (median 17.1 months vs. 8.6 months) (P=0.0002) as compared to PD-L1 <5%.

Conclusion: The data supports the hypothesis that PD-L1 IHC expression could be used to predict clinical benefit of anti-PD-L1 therapy in urothelial cancer patients and has the potential of being used as a predictive biomarker.

11379D

Analyzing biomarkers of cancer immunotherapy (CIT) response using a real-world clinic-genomic database

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Background: Highly discriminating biomarkers of response to cancer immunotherapies (CIT) remain elusive. Characterization of large real-world populations treated with CIT as part of routine care may enable better stratification.

Methods: Patients in the Flatiron Health Analytic Database with non-small cell lung cancer (NSCLC) who underwent comprehensive genomic profiling (CGP) by Foundation Medicine were included (n = 2139). CGP included >340 genes and tumor mutation burden (TMB), stratified into low (TMB-L < 6 mut/MB), intermediate (TMB-I 6-20 mut/MB), and high (TMB-H > 20 mut/MB) tertiles (Johnson, CIR 2016). PD-L1 expression was obtained from results reported to clinicians from multiple labs (using varying antibodies). Genomic data was linked to de-identified electronic health record (EHR) data, from which nivolumab response was measured as overall response rate (ORR = SD, PR, or CR), median duration of therapy (mDOT), and median overall survival (mOS) from advanced diagnosis and from nivolumab initiation.
Results: In patients treated with nivolumab (n = 444, 20.8%), TMB-H predicted longer mDOT than TMB-L (7.5 vs 4.6 months, p < 0.001), mOS from start of nivolumab treatment (median not reached vs 10 months, p < 0.01), and mOS from advanced diagnosis (65 vs 29 months, p < 0.10). In contrast, PD-L1 status (n = 282) was not associated with ORR, DOR, or OS. Among patients negative for PD-L1, TMB-H predicted longer DOR (mDOR 391 vs 166 days, p = 0.08) and higher ORR (100% in TMB-H vs n = 51 vs 62% in TMB-LL; n = 28, p = 0.03). TMB-remained predictive of DOR and OS from nivolumab-start when controlled for histology, age, smoking, gender, and race in multivariate analysis. Multivariate analysis of TMB-H, patients identified two additional genomic predictors of duration on nivolumab: BRAF (HR 0.12, p = 0.04), and BRCA1/2 (HR 0.05, p < 0.01).

Conclusions: Real-world datasets combining clinical outcomes with genomic profiling may enable biomarker discovery in CIT. These data demonstrate the predictive power of TMB, which can augment and significantly improve on the currently approved PD-L1 expression as a predictor of CIT response. They may also enable discovery of novel biomarkers that can identify potential CIT responders among TMB-L populations.

Legal entity responsible for the study: Foundation Medicine, Inc. and Flattor Health, Inc.

Funding: None

Disclosures: A. K. Singavi: Employee - Foundation Medicine, Inc. and Flatiron Health, Inc.


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Background: Pseudo-progression associated with ICI has been well described. HP - characterized by paradoxically accelerated tumor growth rate (TGR) - while on ICI is increasingly being recognized. Preliminary data have reported murine double minute (MDM2/MDM4) amplification as a possible predictive biomarker for HP based on pre-treatment next generation sequencing (NGS) of tumor tissue. We sought to identify patients that hyper-progressed at our institution, characterize the SAs in those patients (pts) and conversely, estimate the incidence of HP in pts with such SAs.

Methods: HP was defined as: 1. progression at first restaging on ICI 2. Increase in tumor size >2-fold increase in TGR. Data were obtained by interrogating our institutional electronic medical record and molecular database (MDB). Next Generation Sequencing (NGS - Foundation Medicine, Cambridge MA) was performed on pre-treatment tumor tissue; DNA was extracted, NGS was performed on hybridized tumor tissue. We sought to identify patients that hyper-progressed at our institution, characterize the SAs in those patients (pts) and conversely, estimate the incidence of HP in pts with such SAs.

Results: 5 pts met criteria for HP, NGS data was available on 4 (80%) pts. Most frequently encountered SAs were MDM2/MDM4 amplifications (amp -50%), EGFR amp (25%) and amp of several genes located on chromosome 11q13 -CCND1, FGF3, FGF4, NOTCH1, SPOP, TP53 (amp -9%). Among patients negative for PD-L1, TMB-H predicted improved clinical outcomes (65 vs 29 months, p < 0.03). TMB remained predictive of DOR and OS from nivolumab-start when controlled for histology, age, smoking, gender, and race in multivariate analysis. Multivariate analysis of TMB-H, patients identified two additional genomic predictors of duration on nivolumab: BRAF (HR 0.12, p = 0.04), and BRCA1/2 (HR 0.05, p < 0.01).

Conclusions: Real-world datasets combining clinical outcomes with genomic profiling may enable biomarker discovery in CIT. These data demonstrate the predictive power of TMB, which can augment and significantly improve on the currently approved PD-L1 expression as a predictor of CIT response. They may also enable discovery of novel biomarkers that can identify potential CIT responders among TMB-L populations.

Table: 1140PD

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Results: CA-170, a first in class oral small molecule dual inhibitor of immune checkpoints PD-L1 and VISTA, demonstrates tumor growth inhibition in pre-clinical models and promotes T cell activation in Phase 1 study


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Background: Programmed-death 1 (PD-1) and V-domain Ig suppressor of T-cell activation (VISTA) are independent immune checkpoints that inhibit T cell function. Preclinical studies demonstrated that dual blockade of these checkpoints can be synergistic. CA-170 is an oral small molecule antagonist of PD-L1 and VISTA, currently undergoing Phase (Ph) 1 clinical testing.

Methods: Pre-clinically, CA-170 inhibition of PD-L1 or VISTA-mediated suppression of T cell function was tested in vitro using human, monkey, or mouse cells. In vivo anti-tumor activity was examined in multiple mouse pre-clinical models. Pts with advanced solid tumors or lymphomas, age ≥ 18, ECOG ≤ 1 and adequate organ function are treated with escalating doses of oral CA-170 daily during Ph 1a. Ph 1b dose expansion will enrich enrollment for selected pt population possibly responsive to this novel inhibitor. Primary objectives: safety, maximum tolerated dose and recommended Phase 2 dose. Secondary objectives: pharmacokinetics and anti-tumor activity. Exploratory endpoints: biomarkers and pharmacodynamic (PD) effects in periphery and tumor.

Results: CA-170 reduces in vitro T cell effector function with activity comparable to that of PD-1 or VISTA blocking antibodies. Oral CA-170 inhibits the growth of mouse syngeneic tumors (B16 melanoma, CT26 and MC38 colon carcinoma), enhances peripheral T cell activation was observed with an increased proportion of circulating CD8⁺ and CD4⁺ T cells expressing activation markers, CD69 and CD134, following oral dosing. Conclusions: These pre-clinical and preliminary clinical PD data warrant the continu-

Clinical Development, Foundation Medicine, Cambridge, MA, USA

1142PD Safety, pharmacokinetics (PK) and pharmacodynamics (PD) data from a phase I dose-escalation study of OX40 agonistic monoclonal antibody (mAb) PF-04518600 (PF-8600) in combination with utomilumab, a 4-1BB agonistic mAb


1Medicine, The Angeles Clinic and Research Institute, Los Angeles, CA, USA, 2Development and Clinical Research, Pfizer Inc, South San Francisco, CA, USA, 3Early Hospitalier Pitie´ Salpetriere, Paris, France, 4Medicine, Columbia University, New York, NY, USA, 5ptomilumab has not demonstrated toxicity beyond that expected from either overall, than PF-8600 alone. Preliminary PK and efficacy data will be shown.

Combination treatment resulted in greater increases in expression of activation and proliferation markers on CD8 memory T cells, in particular, and memory T cell subsets decreased appetite (7.1%) and fatigue (7.1%). Nine (32.1%) G3, 3 (10.7%) G4 and 2 4/5 planned dose cohorts. No drug-related deaths, dose-limiting toxicities, or suspected at time of data cut-off on 30-Jan 2017 (study ongoing), 28 pts had enrolled in 0.1 mg/kg to 3 mg/kg q2w in combination with utomilumab at either 20 mg or 100 mg.

Methods: Primary objectives were to assess dose limiting toxicities (DLTs) in a 6 + 6 dose escalation design and determine RP2D. Eligible pts had metastatic TNBC treated with ≤4 prior lines of chemotherapy OR platinum-resistant recurrent OC treated with ≤5 prior lines of chemotherapy having responded with CR or PR for ≥6 months to 1st line platinum based chemotherapy. Results: The 14 pts (≥18 yrs) enrolled received pembrolizumab 200 mg IV on day 1 and niraparib 200 mg (dose level [DL] 1, n = 7; 2 TNBC, 5 OC) or 300 mg (DL2, n = 7; 3 TNBC, 4 OC) PO on days 1–21 of each 21-day cycle. In DL1, 1 pt had DLT (neutropenia, anemia and thrombocytopenia) and discontinued niraparib but continued pembrolizumab. In DL2, 1 pt had DLT and 1 had DLT-equivalent (both thrombocytopenia); both resumed treatment with 200 mg niraparib and continued pembrolizumab. RP2D was determined as niraparib 200 mg PO daily + pembrolizumab 200 mg IV on day 1 of each 21-day cycle. Based on FDA CDRCT v1.1, 4/9 evaluable OC pts responded; the other 4 pts achieved SD (Table). 1/5 TNBC pts (BRCA wildtype) had SD for 10 cycles. BRCA & PD-L1 status will be announced.

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Methods: Primary objectives were to assess dose limiting toxicities (DLTs) in a 6 + 6 dose escalation design and determine RP2D. Eligible pts had metastatic TNBC treated with ≤4 prior lines of chemotherapy OR platinum-resistant recurrent OC treated with ≤5 prior lines of chemotherapy having responded with CR or PR for ≥6 months to 1st line platinum based chemotherapy. Results: The 14 pts (≥18 yrs) enrolled received pembrolizumab 200 mg IV on day 1 and niraparib 200 mg (dose level [DL] 1, n = 7; 2 TNBC, 5 OC) or 300 mg (DL2, n = 7; 3 TNBC, 4 OC) PO on days 1–21 of each 21-day cycle. In DL1, 1 pt had DLT (neutropenia, anemia and thrombocytopenia) and discontinued niraparib but continued pembrolizumab. In DL2, 1 pt had DLT and 1 had DLT-equivalent (both thrombocytopenia); both resumed treatment with 200 mg niraparib and continued pembrolizumab. RP2D was determined as niraparib 200 mg PO daily + pembrolizumab 200 mg IV on day 1 of each 21-day cycle. Based on FDA CDRCT v1.1, 4/9 evaluable OC pts responded; the other 4 pts achieved SD (Table). 1/5 TNBC pts (BRCA wildtype) had SD for 10 cycles. BRCA & PD-L1 status will be presented.
Adjuvant therapy with autologous dendritic cell (DC) vaccine based on cancer-testis antigens (CaTeVac) in melanoma patients

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Background: Interferon-alpha (IFN) is still a standard and most widely used adjuvant therapy for patients (Pts) with skin melanoma. Nevertheless, the efficacy of this approach is doubtful despite decades of clinical trials. CaTeVac is autologous DC, derived from the peripheral mononuclear cells of the patient, loaded with melanoma cell lines with high expression of cancer-testis antigens. We compared cohort of Pts receiving adjuvant therapy with CaTeVac with a cohort of consecutive Pts in our center who received IFN in the adjuvant setting.

Methods: Pts with morphologically proven melanoma received CaTeVac or IFN. CaTeVac was injected subcutaneously in doses from 5 to 20*10^6 cells per cycle (C.) in the following regimens: C.1-14 days, C.2-21 days, C.3-28 days. After a year of therapy Pts were allowed to receive additional cycles: C.15-18 (3 mo each) and C.19-20 (6 mo each). Each C. consisted from cyclophosphamide 300 mg injection on day 1 and CaTeVac injection on day 4. In control group received IFN until progression, toxicity or at least 1 year of therapy whatever comes first. Both groups of patients were followed with the same clinical and laboratory methods and in the same time intervals.

Results: Ninety Pts treated from 2009 to 2016 were included in the study: 48 received CaTeVac, 42 – IFN (2-high doses of IFN, 36 – low doses of IFN, 4 – IFN with dose escalation from 3 MIU until maximum tolerated dose achieved). Median of follow-up was 23 mo. Patients with stage III and IV were presented more often in CaTeVac group (68% and 4%, respectively). Stage II patients composed 28% of IFN group, none were in CaTeVac group; X2 test for stage distribution was 8.74 (p = 0.014). Median of overall survival was 79.8 mo in IFN group and was not reached in CaTeVac group (p = 0.352) with plateau at 38% after 41 months.

Conclusions: However, while at least 30% of Pts show positive response to ICI treatments, melanoma cell lines with high expression of cancer-testis antigens. We compared cohort of Pts receiving adjuvant therapy with CaTeVac with a cohort of consecutive Pts in our center who received IFN in the adjuvant setting.

Clinical trial identification: NCT02482090

Legal entity responsible for the study: Center for Cancer Immune Therapy, Department of Hematology and Department of Oncology, Herlev and Gentofte Hospital 2730 Herlev, Denmark

Funding: Center for Cancer Immune Therapy, Herlev and Gentofte Hospital Department of Oncology, Herlev Hospital and Gentofte Hospital University of Copenhagen The Danish Cancer Society OvaCare

Disclosure: All authors have declared no conflicts of interest.

Table: 1143PD

<table>
<thead>
<tr>
<th>Best response</th>
<th>Time to response</th>
<th>Cycle (weeks)</th>
<th>Time on study Cycle</th>
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<td>11+</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>6 (18)</td>
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<td>SD</td>
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* + = ongoing
Assessed every 3 cycles

Conclusions: This study established a RP2D, and showed preliminary efficacy of mirparb and pembrolizumab for treatment of heavily pretreated TNBC or platinum-resistant OC. No significant overlapping toxicity was noted. A Phase 2 study is currently enrolling. Supporting translational work funded by SU2C.

Clinical trial identification: NCT02657889

Legal entity responsible for the study: TESARO, Inc.

Funding: TESARO, Inc. and Merck & Co.


Adoptive cellular therapy with tumor-infiltrating lymphocytes for patients with metastatic ovarian cancer: A pilot study

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Background: Metastatic ovarian cancer (OC) is often diagnosed at an advanced stage and treated with standard platinum-based chemotherapy after which the majority of patients will experience recurrent/progressive disease with a poor prognosis. Adoptive cell therapy (ACT) with tumor-infiltrating lymphocytes (TIL) has shown impressive results in malignant melanoma, but has only been investigated scarcely in other cancers. This pilot study has tested TIL based ACT in patients with metastatic OC. Preliminary data has previously been presented at the European Society for Medical Oncology (ESMO), the Society of Immunotherapy of Cancer (STIC) and the Cancer Immunotherapy & Immunomonitoring (CITIM) conferences. In this abstract the final data has previously been presented at the European Society for Medical Oncology (ESMO), the Society of Immunotherapy of Cancer (STIC) and the Cancer Immunotherapy & Immunomonitoring (CITIM) conferences. In this abstract the final results of the study is presented.

Methods: Patients with platinum-resistant metastatic OC were treated with an infusion of TIL, preceded by standard lymphodepleting chemotherapy (Cyclophosphamide 60 mg/kg for 2 days and Fludarabine 25 mg/m^2 for 5 days) and followed by stimulation with a continuous IL-2 infusion in accordance with the decrescendo regimen for up to 5 days. Stem cell harvest was performed before TIL therapy. Primarily, the feasibility and tolerability of the treatment was assessed. Secondly, potential immune responses against tumor cells were monitored and objective response of the treatment was described.

Results: Only expected and manageable toxicities related to the treatment were observed. All patients had stable disease (SD) for a minimum of 3 months with 4 patients experiencing progressive disease (PD) at this time point. The last two patients had SD for 5 months. Most antitumor reactivity was observed in expanded TIL, but not in peripheral blood lymphocytes (PBL) collected after treatment.

Conclusions: ACT with TIL in combination with decrescendo IL-2 is feasible and tolerable in patients with metastatic OC with only expected and manageable toxicities. Methods of altered TIL expansion or combining TIL therapy with checkpoint inhibitors in future studies could possibly enhance the truly transient clinical responses observed in this pilot study.
A phase I/II safety study of tisotumab vedotin (HuMax-R-ADC) in patients with solid tumors

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Methods: dose-escalation part.

Results: Twenty-seven pts were enrolled across 8 dose cohorts (0.3-2.2 mg/kg).

Conclusions: Tisotumab vedotin demonstrated a manageable toxicity profile. Recommended Ph I dose was identified as 2.0 mg/kg q3Wk. Biological activity included SD in 13 pts and 1 pt with prolonged PR (cervical cancer). TF was found widely expressed across investigated indications by IHC. Data warrant further exploration in solid tumors.

Clinical trial identification: NCT02001625, release date November 14, 2013

Legal entity responsible for the study: Gennab A/S

Funding: Gennab A/S

Disclosure: S. Hong: Research/Grant Funding: Bayer, Lilly, Genentech, LOXO, Pfizer, Amgen, Mirati, Ignyta, Merck, Daiichi-Sankyo, Eisai Travel, Accommodations, Expenses: MiRNA, LOXO Consulting Role: Bayer, Baxter, Guidedpoint Global Other: Oncoreponse (founder). R. Coleman: Member of Gennab’s Advisory Board for Tisotumab vedotin. J. de Bono: Employee of The institute of Cancer Research, Served on Gennab Advisory Board, have served as advisor on advisory boards for multiple in industry partners incl: AstraZeneca, Daiichi-Sankyo, Genentech, GSK, Merck, Pfizer, Sanofi, Taiho a.o. S. Libby: Employee of Gennab and hold stocks in the company. All other authors have declared no conflicts of interest.

1148PD Immunotherapy in patients with concurrent solid organ transplant, HIV, and Hepatitis B and C


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Background: Anti PD-1/PD-L1 (PD1) agents are being used to treat various tumor types. Most trials have excluded patients (pts) who have had a solid organ transplant (SOT), HIV, or Hepatitis (Hep) B and Hepatitis C. The safety and efficacy of PD1 in this setting is unknown.

Methods: Pts treated at 16 centres that had a transplant, HIV, Hep B/C were included. Pts demographics, tumour characteristics, toxicity, response and survival data, and the effect on the underlying condition were collected.

Results: 42 pts were identified, 29 with melanoma, 6 bladder carcinoma (BC), 2 hepatocellular carcinoma (HCC), 2 renal cell carcinoma (RCC), 2 mesothelioma (meso), and 1 gastric carcinoma, glioblastoma multiforme (GBM) and non-small cell lung cancer (NSCLC). 5 pts with SOT (4 renal, 1 liver) had melanoma received pembrolizumab; 3 had progressive disease (PD), 1 partial response (PR), and the pt with liver transplant had graft rejection and died from this after 1 dose. 1 pt with BC received nivolumab; 1 pt with metastatic viral load. 8 pts had pembrolizumab (7 melanoma, 1 HCC), 2 nivolumab (1 melanoma, 1 RCC) and 1 atezolizumab (RCC). No pt had loss in viral control or immune reconstitution inflamma- tory syndrome. 2 had complete response (CR), 1 PR, 4 stable disease (SD) and 4 PD. 14 pts had Hep C; 9 with detectable viral load, 6 on anti-viral therapy and 5 with cirrhosis. 6 received pembrolizumab (5 melanoma, 1 meso), 7 nivolumab (4 melanoma, 1 each of NSCLC, BC, RCC) and 1 atezolizumab (BC). No pt had loss in viral control. 1 developed grade 3 colitis but no one developed hepatitis. 2 had grade 3 hepatitis and 1 developed grade 4 hepatitis. 1 pt had CR, 9 SD and 3 PD. 12 pts with Hep B, 8 with detectable viral load, 6 on anti-viral therapy and none with cirrhosis. 8 had pembrolizumab (5 melanoma, 1 each of GBM, gastric carcinoma and meso), 4 nivolumab (2 melanoma, 1 BCC, 1 RCC). No pt had loss in viral control. 1 had CR, 1 PR, 8 SD and 2 PD. None of Hep B or Hep C pts suffered immune related hepatitis.

Conclusions: Immunotherapy has the ability to have activity in patients with SOT, HIV and Hep B/C. It can be given to renal transplant pts without rejection, however this is not universal. PD1 does not appear to adversely affect the viral control in Hep B and Hep C pts. Legal entity responsible for the study: Human ethics approved protocol at Melanoma Institute Australia

Funding: None

Disclosure: L. Zimmer: Honoria: Roche. S. Goldberg: Research funding from the University of Sydney Hospital and received travel grant support from Novartis, Roche, MSD and Bristol-Myers Squibb. M. Millward: grant support from GlaxoSmithKline during the conduct of the study and other support from GlaxoSmithKline. V. Atkinson: advisory boards and received travel support and speaker’s fees from Bristol-Myers Squibb, Novartis and MSD. GVL is a consultant advisor to Agena, Merck MSD, Novartis and Roche received honoraria from Bristol-Myers Squibb, Novartis and Merck MSD. P.A. Asciento: receiving consulting fees from Bristol-Myers Squibb, Roche, GSK, MSD, Ventana Medical Systems, Novartis, and Amgen, honoraria from Bristol-Myers Squibb, Roche, and GSK, and grant support to his institution from Bristol-Myers Squibb, Roche, and Ventana Medical Systems. C. Garbe: Advisory board: AMGEN, Bristol-Myers Squibb, GSK, MSD, Novartis and Roche. M. Millward: Bristol-Myers Squibb, Memorial Sloan Kettering Consulting. Ro. Guttmann: Received project support from Novartis Pharma and Pfizer Lecture honoraria from Novartis Pharma and Pfizer. D.B. Johnson: personal fees from Genoptics and Bristol-Myers Squibb. G.V. Lang: personal fees from GlaxoSmithKline during the conduct of the study and personal fees from Roche, Novartis, Amgen, and Bristol-Myers Squibb. A.M. Menzies: honoraria from Bristol-Myers Squibb and Novartis, and has sat on advisory boards for MSD and Chugai. All other authors have declared no conflicts of interest.
Annals of Oncology

1149P

Results of the randomized, placebo-controlled phase I/II trial of CV9104, an mRNA based cancer immunotherapy, in patients with metastatic castration-resistant prostate cancer (mCRPC)

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1Department of Oral & Maxillofacial Surgery, Graduate School of Medical Sciences, R. Cathomas7, C. Gru¨ llich8, Y. Loriot9, S.L. Perez Gracia10, S. Gillessen11, U. Klinkhardt12, Oncology, Studienpraxis Urologie, Reutlingen, Germany, 3Clatterbridge Cancer Center, Germany, 13Biostatistics, Cogitars GmbH, Heidelberg, Germany, 14Biomarkers & Immunoanalysis, CureVac AG, Tübingen, Germany

Background: CV9104 is a novel prostate cancer immunotherapy based on sequence-optimized, free and proteamine-complexed mRNA encoding the antigens PSA, PSMA, PSCA, STEAP1, PAP and MUC1. Safety and immune responses to the predecessor therapy CV9103 encoding 4 of the antigens have been described previously. We assessed whether immunotherapy with CV9104 on top of standard care (SOC) results in longer overall survival than placebo plus standard of care in patients with mCRPC.

Methods: After completion of a safety lead-in phase, 1 men with chemo-naive, oligostatic/asymptomatic mCRPC without visceral metastases were randomized 2:1 to intra- dermal CV9104 or placebo (P). Double-blinded treatment was continued until progression under SOC therapy or toxicity. The primary endpoint (P) was overall survival (OS). Key secondary endpoints included radiographic progression-free survival (rPFS), other PFS endpoints (from randomization until disease progression, i.e., index progression or death; “on PFS2 from start of SOC therapy to second progression”), time to symptomatic progression and visceral and humoral immune responses.

Results: 197 patients (pt) were randomized 2:1 to either CV9104 (n = 134) or P (n = 63). Pt characteristics, median number of administrations and first subsequent SOC therapies were well balanced between the arms. No significant difference in OS was found, median (m) OS was 35.5 months (mo) [28.8–NE] in the CV9104 arm vs. 33.7 mo [28.7–NE] in the P arm (hazard ratio [HR] 1.1, 95% CI 0.70–1.76; one-sided p = 0.33). There were also no significant differences in the rPFS endpoints and time to symptom progression. Incidence of Grade ≥3 AEs (51.1% vs. 59.7%) and serious AEs (44.9% vs. 47.9%) was similar in both arms, injection site reactions and flu-like symptoms were more frequent in the CV9104 arm.

Conclusions: CV9104 did not improve OS compared to placebo. Additional clinical outcomes, such as analyses of cellular and humoral immune responses will be presented and impact on further development will be discussed.

Clinical trial identification: EudraCT number: 2011-00614-14

Legal entity responsible for the study: CureVac AG

Funding: Study Sponsor: CureVac AG


1150P

Phase II clinical trial of peptide vaccination for advanced head and neck cancer patients induced immune responses and prolonged OS


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Background: The carcinoembryonic antigen glypican-3 (GPC3) is a good target of anticancer immunotherapy against pediatric solid tumors expressing GPC3. In this non-randomized, open-label, phase I clinical trial, we analyzed the safety and efficacy of GPC3-peptide vaccination in patients with pediatric solid tumors.

Methods: We conducted a phase I study of pediatric patients with solid tumors. GPC3 is a target of anticancer immunotherapy against some pediatric solid tumor especially hepatoblastoma. Vaccinations were carried out biweekly from the first until disease progression with the primary endpoint being the safety of GPC3-peptide vaccination and the secondary endpoints being immune response, as measured by interferon (IFN)-γ enzyme-linked immunosorbent assay and Dextrameter staining, and the clinical outcomes of tumor response, progression-free survival and overall survival.

Results: A total of 18 patients (7 hepatoblastoma, 4 rhabdomyosarcoma, 3 brain tumor, 1 MRT, 1 pancreaticoblastoma, 1 Wilm tumor, 1 germ cell tumor) were enrolled from 5 hospitals, all cases showed no dose-limiting toxicity (DLT), which was the primary endpoint of this trial. No grade 3–4 hematological and non-hematological toxicity due to GPC3 vaccine therapy occurred. Clinical benefit ratio was 66.7% with six long SD (SD > 18) (MST 4.9 vs. 3.5 month, respectively, p < 0.05). One of the patients exhibited a complete response. In the A24(+)-vaccinated group, the ELISPOT assay identified LY6K-, CDCA1- and IMP3-specific CTL responses in 85.7%, 64.3% and 42.9% of the patients, respectively. The patients showing LY6K-, CDCA1-specific CTL responses demonstrated a longer OS than those without CTL induction. Moreover, the patients exhibiting CTL induction for multiple peptides demonstrated better clinical responses.

Conclusions: The immune response induced by this peptides vaccine may improve the progression free survival (PFS) and overall survival (OS).

Legal entity responsible for the study: AKO hosono

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1151P

Phase I study of glypican-3 derived peptide vaccine therapy for patients with refractory pediatric solid tumors

A. Hosono1, T. Yoshikawa2, N. Tsuchiya3, N. Fujinami4, K. Sat05, S. Mizuno6, T. Nakatsura7

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Background: The carcinoembryonic antigen glypican-3 (GPC3) is a good target of anticancer immunotherapy against pediatric solid tumors expressing GPC3. In this non-randomized, open-label, phase I clinical trial, we analyzed the safety and efficacy of GPC3-peptide vaccination in patients with pediatric solid tumors.

Methods: We conducted a phase I study of pediatric patients with solid tumors. GPC3 is a target of anticancer immunotherapy against some pediatric solid tumor especially hepatoblastoma. Vaccinations were carried out biweekly from the first until disease progression with the primary endpoint being the safety of GPC3-peptide vaccination and the secondary endpoints being immune response, as measured by interferon (IFN)-γ enzyme-linked immunosorbent assay and Dextrameter staining, and the clinical outcomes of tumor response, progression-free survival and overall survival.

Results: A total of 18 patients (7 hepatoblastoma, 4 rhabdomyosarcoma, 3 brain tumor, 1 MRT, 1 pancreaticoblastoma, 1 Wilm tumor, 1 germ cell tumor) were enrolled from 5 hospitals, all cases showed no dose-limiting toxicity (DLT), which was the primary endpoint of this trial. No grade 3–4 hematological and non-hematological toxicity due to GPC3 vaccine therapy occurred. Clinical benefit ratio was 66.7% with six long SD (SD > 18) (MST 4.9 vs. 3.5 month, respectively, p < 0.05). One of the patients exhibited a complete response. In the A24(+)-vaccinated group, the ELISPOT assay identified LY6K-, CDCA1- and IMP3-specific CTL responses in 85.7%, 64.3% and 42.9% of the patients, respectively. The patients showing LY6K-, CDCA1-specific CTL responses demonstrated a longer OS than those without CTL induction. Moreover, the patients exhibiting CTL induction for multiple peptides demonstrated better clinical responses.

Conclusions: The immune response induced by this peptides vaccine may improve the progression free survival (PFS) and overall survival (OS).

Legal entity responsible for the study: Yoshihiro Yoshitake

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1152P

Phase I study of HSPI010-derived peptide vaccine for patients with advanced esophageal cancer/colo- rectal cancer


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Background: The HSPI010 protein has been identified in pancreatic cancer by the SEREX method, and this protein has also been reported to play a role in controlling
apoptosis in cancer cells. HSP105 is highly expressed in various human cancers, including colorectal cancer, esophageal cancer, pharyngeal cancer, pancreatic cancer, breast cancer, and melanoma. We have therefore identified the respective HSP105-derived peptides that bind to HLA-A2 and HLA-A12 (EP136806, HLA-A12; EP136806, HLA-A2; EP2591641, US9,404,925). We investigated the safety and efficacy of HSP105-derived peptide vaccine for patients (pts) with advanced esophageal cancer/colorectal cancer.

Methods: We conducted a multicenter phase 1 study of HSP105-derived peptide vaccine for pts with advanced esophageal cancer/colorectal cancer. The recommended dose is determined based on the incidence of dose-limiting toxicity (DLT) during phase 1a (P1a). Pts will then be added in phase 1b (P1b) to investigate the safety and efficacy of the vaccine. The vaccine was injected intradermally every 7 days. The primary objective of this study was to evaluate DLT (P1a), response rate (P1b). Progression-free survival, treatment failure rate, and toxicity were also evaluated as secondary objectives. As exploratory endpoint, immunological effect was investigated.

Results: A total 30 pts (HLA-24 group 15 pts) were enrolled and grouped into level 1 which received intradermally administration of peptide vaccine (emulsifying agent: Montanide ISA 51 VG) 3 mg/body. No DLT occurred and no major safety problems were reported throughout the trial. Although pts with objective clinical efficacy was not apparent, 7 pts showed stable disease 2 months after initiation of treatment. The HSP105-derived peptide vaccine induced HSP105-specific CTL response in 15 pts (50%) of 30 pts. Additionally, we established several HSP105 peptide-specific CTL clones derived from vaccinated and a HSP105 peptide by single cell sorting using Dextramer or anti-CD107a antibody.

Conclusions: Although objective clinical efficacy was not apparent, HSP105-derived peptide vaccine appears well tolerated with minimal local toxicity.

Clinical trial identification: Protocol number: UMIN000017809, Release date: Jun 22, 2015

Legal entity responsible for the study: National Cancer Center


Disclosure: All authors have declared no conflicts of interest.

An observational clinical study with RAS peptide vaccine TG01 evaluating immune response, safety and overall survival in patients with non-resectable pancreatic cancer

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Background: The study evaluated the immune response, safety and survival of the TG01/GM-CSF vaccine, an antigen-specific cancer immunotherapy consisting of 7 RAS peptides targeted to KRAS mutated pancreatic adenocarcinoma, in treatment naive non-resectable pancreatic cancer patients (pts). TG01/GM-CSF was recently reported to elicit immune response and increased survival in resectable pancreatic pts (ASCO 2017).

Methods: 25 treatment naive non-resectable pancreatic cancer pts were included with TG01/GM-CSF at week 1, 2, 3, 4, 6, 10 (immunisation period) followed, after a 3 months pause, by a booster period of four weekly administrations. Pts were followed up for up to 12 months from 1st dose of TG01/GM-CSF. Immune response was evaluated by Delayed Type Hypersensitivity (DTH) skin reaction test, (S)AEs recorded throughout the study and survival data calculated using Kaplan-Meier.

Results: 14/25 pts (56%) had a positive DTH by week 10. The TG01/GM-CSF-treat ment was well tolerated with no reports of allergic or other adverse hypersensitivity reactions. 13 pts experienced 19 SAEs; 5 were due to disease progression, 13 were deaths due to disease progression, and one was treatment related (hyperglycemia). Median survival (MS) from first administration of TG01/GM-CSF was for all treated pts (n = 25) 4.5 months, for DTH responders (n = 14) 5.1 months and for DTH non-responders (n = 11) 3.6 months. For the DTH responders the result compares favorably with untreated patients (MS = 3.7 months)1. At 1 year, 4 pts of whom 3 DTH responders were alive. 1. Palmer KR et al., Br J Surg: 81, 882-885 (1994).

Conclusions: In pts treated with TG01/GM-CSF monotherapy, immune response was recorded in 56% of the pts, results that correspond with data from a Phase II trial with a similar RAS peptide vaccine in non-resectable pancreatic pts. Even though not statistically significant, the results indicate increased survival for the immune responders. In the otherwise incurable disease, the non-resectable pancreatic pts may therefore benefit from immunisation with TG01/GM-CSF RAS peptide vaccine with few side effects. 2. Giertsen M et al., Int J Cancer: 92, 441-450 (2001).

Clinical trial identification: Protocol CTN RAS 90810, 20.05.1998, Norway

Legal entity responsible for the study: Norsk Hydro ASA, Oslo, Norway

Funding: Norsk Hydro ASA, Oslo, Norway

Disclosure: J. A. Eriksen: Employed as chief technology innovation officer of Targovax ASA and holds a patent on the UV1 peptide vaccine patent. W. Rasch: Holder owns stock in Ultimovacs AS and is an employee in the same company. E.M. Inderberg: Inventor of the UV1 vaccine patent. W. Rasch. Holder owns stock in Ultimovacs AS and is an employee in the same company. J. Bjørheim: Employee at Ultimovacs AS. All other authors have declared no conflicts of interest.

Results of an open label randomized phase II trial of CV9104, an mRNA-based multivalent cancer immunotherapy in patients (pts) with intermediate or high risk localized prostate cancer (PC) undergoing radical prostatectomy (RPE)

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Background: CV9104 is a multivalent mRNA-based active cancer immunotherapy containing sequence-optimized free and protamine complexed mRNA coding for six prostate cancer associated antigens (PSA, PSMA, PSCA, STEAP1, PAP and MUC1). CV9104 has been investigated in a placebo controlled Phase III study in pts with metastatic castrate-resistant PC. Administration of mRNA-based immunotherapy by needle free jet devices has been shown to improve antigen expression and immunogenicity vs needle injection in preclinical models. The purpose of this study was to evaluate immune responses and safety of CV9104 administered by conventional intraderal (ID) injection or with a needle-free ID (nID) injection device in pts with intermediate/ high risk localized PC.

Methods: 48 pts with intermediate or high risk localized PC and an indication to undergo RPE were randomized in a 1:1:1 ratio to receive presurgical CV9104 by nID injection (960 µg mRNA per administration) (A), or ID injection (1920 µg mRNA per
Results: 48 pts were randomized (A: 15; B: 17; C: 16). Treatment with CV9104 was well tolerated using the nFlD or cFlD injection, with a safety profile similar to other previous mRNA-based cancer immunotherapies. Cellular and humoral immune responses including responses per antigen and additional biomarker results will be presented.

Clinical trial identification: EuDraCT Number: 2013-004489-32

Legal entity responsible for the study: CureVac AG

Funding: Sponsored Clinical Trial: CureVac AG


1156P Italian nivolumab expanded access programme: real-world results in non-squamous non-small cell lung cancer patients

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Background: Nivolumab monotherapy has shown survival benefit in patients (pts) with different, including previo usly untreated NSCLC. Nivolumab 3 mg/kg was administered intravenously every 2 weeks to a maximum of 24 months. Pts included in the analysis had received at least 1 dose of nivolumab and were monitored for adverse events (AE) using Common Terminology Criteria for Adverse Events. Results: In total, 1598 Italian pts participated in the EAP across 168 centers. Baseline characteristics of pts were representative of the population with non-squamous NSCLC, in the advanced disease setting. With a median follow-up of 7.8 months (1-219) and a median of 7 doses, the overall response rate (ORR) was 18%, including 10 pts (<1%) with complete response and 280 pts (17%) with partial response. Stable disease has been defined for 414 pts (26%) and totally 279 patients were treated beyond progression. Of March 2017, median overall survival (OS) was 11 months (range: 10.0-12.0). Response rates and survival were comparable among pts regardless age (<75 years), presence of brain metastasis and number of prior therapies. Overall, amongst 1588 pts, 1254 discontinued treatment for any reason, with only 80 pts (5%) who discontinued treatment due to related adverse events. Conclusions: To date, this is the largest clinical experience with nivolumab in a real-world setting. These preliminary EAP data confirm that nivolumab seems to be an effective and safe therapy for pts with non-squamous NSCLC, supporting its use in current clinical practice. Clinical trial identification: CA209-966

Legal entity responsible for the study: Prof. Lucio Cinar

Funding: Bristol-Myers Squibb

Disclosure: F. Grossi: Consulting or Advisory Role: Bristol-Myers Squibb, Boehringer Ingelheim, Merck Sharp & Dohme, Pfizer, Fabre, AstaZenna, Roche. F. De Marinis: Consulting or Advisory Role: Bristol-Myers Squibb, AstraZeneca, Roche. H.J. Soto: Consulting or Advisory Role: Bristol-Myers Squibb. G. Puppo: F. Grossi Consulting or Advisory Role: Bristol-Myers Squibb, Pfizer, AstraZeneca, Novartis Pharma. M.R. Migliorino: Honoraria: Bristol-Myers Squibb, Boehringer Ingelheim, AstaZenna Consulting or Advisory Role: Bristol-Myers Squibb, Boehringer Ingelheim, AstaZenna. G. Tonini: Consulting or Advisory Role, Pfizer Fabre, Molteni Farmaceutici, Novartis Pharma KK, Roche. F. Cognetti: Consulting or Advisory Role: AMTene Research Funding Company: Genomic Health A. Sappolla: Travel, Accommodations, Expenses: IBSA. E. Cortesi: Honoraria: Jansen Corp Consulting or Advisory Role: Nixtx Medical. All other authors have declared no conflicts of interest.

1157P Correlation and differences in Effect sizes between Progression Free Survival (PFS) and Overall Survival (OS) among PD-1 inhibitors

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Background: Programmed death 1 (PD-1) inhibitors, such as nivolumab and pembrolizumab, have now been approved for various cancers based on results from pivotal randomized controlled trials (RCTs). These drugs are known for unconventional response patterns with varying effects on PFS and OS. We aimed to compare the correlation between PFS and OS and evaluate the differences in treatment size between PFS and OS for PD-1 inhibitors.

Methods: We carried out a systematic search on PubMed and conference abstracts for RCTs of nivolumab and pembrolizumab versus non-immunotherapy control and obtained data on median PFS, median OS for both arms and hazard ratio (HR) and confidence intervals (CI) for PFS and OS. We evaluated the correlation between PFS and OS as well as between Delta (PFS) and Delta (OS). We also evaluated the ratio of HR of PFS to HR of OS for each trial (HR and obtained a summary RHR by random-effects meta-analysis across trials.

Results: Of 52 studies identified, a total of 11 phase 3 RCTs met the eligibility criteria. However, 2 trials didn’t have data on OS. So our analysis includes 9 RCTs that had data on both PFS and OS (6 Nivolumab, 3 Pembrolizumab). There was no significant correlation between PFS and OS (r = 0.676, R2 = 0.457, P = 0.095) or between Delta (PFS) and Delta (OS) (r = 0.474, R2 = 0.225, P = 0.282). Using random-effects meta-analysis, treatment effects were in general 19% higher for OS than PFS (HR 1.19, 95% CI 1.07 to 1.32, p = 0.081). There was no statistical evidence for lack of homogeneity (I2 = 0.9%, p = 0.850) and thus, subgroup analysis were not conducted. PFS and OS were discordant for 5 RCTs (3 Nivolumab, 2 Pembrolizumab) and in all these 5 RCTs, OS was significant but PFS was not. All RCTs (n = 3) showing benefit for PFS also showed benefit for OS. Only one RCT was negative for OS.

Conclusions: Unlike targeted therapies where benefit in PFS may translate to OS, treatment effect sizes in RCTs of PD-1 inhibitors were greater for OS than PFS. The benefit in OS was poorly captured by PFS. There was no correlation between PFS and OS. OS should remain the standard endpoint for PD-1 inhibitor RCTs unless better surrogate endpoints such as improvement in progression-free survival or OS-based PFS are introduced and validated.

Legal entity responsible for the study: The authors

Funding: None

Disclosure: Y. Ando: Reports grants and personal fees from Taiho Pharmaceutical Co., Ltd., and personal fees from Merck Serono Co., Ltd., Otsu Pharmaceutical Co., Ltd and Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

1158P Is objective response rate (ORR) a valid primary endpoint in phase 2 trials (Ph2) of immune checkpoint inhibitors (ICI) for advanced solid cancers?

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Background: ORR is commonly used as the primary endpoint in Ph2. ICI have different mechanisms of action to chemotherapy or molecular targeted agents (MTA). The validity of ORR as a surrogate for progression-free survival (PFS) and overall survival (OS) with ICI is uncertain and may differ by tumor type. We performed a meta-analysis of randomized controlled trials (RCTs) in advanced solid cancers that compared ICI to chemotherapy, MTA or placebo to address this question. 

Methods: We performed a literature search to determine the current Ph2 designs used in ICI trials. Efficacy data from single-arm trials and RCTs were extracted. Amongst the RCTs, correlations between ORR odds ratio (OR) with PFS hazard ratio (HR) and OS HR were examined for between randomized arms comparisons. Correlations within ICI treatment arms of the RCTs between ORR with PFS and OS rates were also studied. Using data from the RCTs, multivariable models that explained the relationships

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between ORR, 6-month PFS and 12-month OS rates were developed and their predictive performances validated in the single-arm trials.

**Results:** Of 87 PFSs identified, most were single arm design (68%), and only 10% were RCTs with concurrent standard of care arms. ORR was the most common (80%) primary endpoint, and PFS was uncommon (8%). A total of 20 RCTs (4 PD-1 and 16 PD-L1 trials) with mature data were examined. There were 25 treatment comparisons in 8 different tumors (non-small cell lung cancer 44%, melanoma 24%). For RCTs in all tumors, the correlations (ρ) between ORR OR with PFS HR, ORR OR with OS HR, and PFS HR with OS HR were 0.63, 0.57, and 0.42 respectively. Within the ICIs arms, re- between ORR with 6-month PFS, ORR with 12-month OS, and 6-month PFS with 12- month OS were 0.37, 0.08 and 0.74 respectively. In the single-arm trials dataset, we were able to accurately predict 12-month OS using the actual 6-month PFS with the multivariate model developed from our RCTs dataset. Conversely, when ORR was used to predict 6-month PFS or 12-month OS, there was poor agreement between actual and predicted results.

**Conclusions:** These data do not support the use of ORR as a surrogate for OS in ICI tri- als. In future ICi PFS, 6-month PFS should be the primary endpoint rather than ORR.

**Legal entity responsible for the study:** Not applicable

**Funding:** None

**Disclosure:** M. Friedlander: Receives personal fees and grants with an advisory board

**None**

**These data do not support the use of ORR as a surrogate for OS in ICI trials.**

**Background:**

Objective response rate (ORR) is widely used in clinical trials to predict 6-month PFS or 12-month OS, there was poor agreement between actual and predicted results. Conversely, when ORR was used to predict 6-month PFS or 12-month OS, there was poor agreement between actual and predicted results.

**Conclusions:** These data do not support the use of ORR as a surrogate for OS in ICI trials. In future ICi PFS, 6-month PFS should be the primary endpoint rather than ORR.

**Legal entity responsible for the study:** None

**Funding:** None

**Disclosure:** All authors have declared no conflicts of interest.

**Methods:** Clinical trials involving monotherapy with PD-1 or PD-L1 antibody in cancer patients published before April 1, 2017 were reviewed, and treatment related AE data were extracted. Meta-analysis of AE rates was done by Comprehensive Meta-Analysis (v2) using a random effects model. Average AE rate (Total AE No./Total Patient No.) was calculated in Microsoft Excel.

**Results:** 63 studies involving 10592 patients were included: 27 on nivolumab, 23 on pembrolizumab, 8 on atezolizumab, 4 on avelumab, and 1 on BMS-936559. Treatment related AE rates were summarized in the Table. In meta-analysis, all grade AE (AEx) rates (>20%), pruritus, rash, diarrhea, nausea (18-20%), decreased appetite, arthralgia, viti- ligo, pyrexia, hypothyroidism, and asthma (5-10%). Most common AEx included hypotenatremia, lymphopenia, and fatigue (>5%).

**Conclusions:** Common AEs of anti-PD-1/PD-L1 therapy were primarily constitutional and gastrointestinal. Most grade 3-4 AE rates were <1%. Rates of immune-related AE were low. Treatment related death was rare, and pneumonitis was the most common cause.

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**Abstracts**

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**412P**

Long term survival in patients responding to an Anti-PD-1/PD-L1 therapy and disease outcome upon treatment discontinuation

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**Background:** The long-term outcome of cancer patients responding to an anti-PD-1/ PD-L1 immunotherapy (IT) remains unknown. This study aimed to describe the long-term survival of patients responding to anti-PD-1/PD-L1 monotherapy across multiple cancer types.

**Methods:** 306 patients treated with an anti-PD-1 or PD-L1 monotherapy in a phase 1 trial at Gustave Roussy were retrospectively analyzed over a period of 5 years. Major inclusion criteria at least 18 years-old, performance status 0-1, at least 1 infusion, inclusion criteria were: at least 18 years-old, performance status 0-1, at least 1 infusion, and at least 18 months after treatment discontinuation: 6 months). Clinical and biological factors associated with response, long term survival, and secondary refractory disease will be reported at the ESMO meeting.

**Conclusions:** This study shows that, across cancer types, patients with objective tumor response under anti-PD-1/PD-L1 immunotherapy have a high level of overall survival. Best survivals are seen with complete responses (no deaths in our cohort). Complete response rates might be a good short term surrogate marker for overall survival benefits. Clinical trials aiming at putting patients with partial responses under immunotherapy into complete responses should be assessed in a near future.

**Legal entity responsible for the study:** Gustave Roussy

**Funding:** None

**Disclosure:** All authors have declared no conflicts of interest.

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**416P**

Meta-Analysis of Anti-PD-1/PD-L1 Therapy Related Adverse Events in Clinical Trials


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**Background:** SCHOLAR-1 (Crump, ASCO 2016) is a large, pooled analysis of nivolumab and demonstrated poor outcomes: objective response rate (ORR) = 26%; complete response (CR) = 8%. ZUMA-1 is the first, multicenter trial of anti-CD39 CAR T cells (axi-cel) in patients enrolled and reported positive results: ORR = 82%; CR = 54%. This is a comparative analysis of outcomes from ZUMA-1 and SCHOLAR-1 after adjusting for imbalance in key covariates of patients enrolled.

**Methods:** Eligible pts for both studies had nHL (stable disease ≤ 6 mos with ≥ 4 cycles frontline or ≥ 2 cycles later-line therapy, progressive disease as best response, or relapse ≤ 12 mos post autologous stem cell transplant). Standardized analyses were performed to account for other baseline covariates that were imbalanced between the studies despite similar inclusion criteria. These analyses equally weighted the proportions of patients with select prognostic covariates between the two studies. The pre-specified covariates selected for weighting were refractory subgroup and occurrence of SCT after refractory status. Sensitivity analyses included additional covariates.

**Results:** 101 ZUMA-1 pts received axi-cel; SCHOLAR-1 included data from 508 pts. Baseline characteristics for each study are listed in the Table. ZUMA-1 median follow-up was 8.7 mos. Using the standardized analysis, the estimated ORR and CR rates in SCHOLAR-1 were 20% and 6%, respectively. Standardized 6-mo survival rate for SCHOLAR-1 was 35%. Risk of death in ZUMA-1 was reduced by 77% relative to SCHOLAR-1 (P < .0001).
Background: Immune checkpoint blockade appears to be a practicable option of treatment for patients with non-small cell lung cancer (NSCLC) with poor performance status. However, results have been mixed so far. Therefore, we aimed to examine the potential of nivolumab in elderly patients with advanced NSCLC.

Methods: We performed a retrospective analysis of patients treated with nivolumab at our centre from January 2016 to December 2017. Elderly patients were defined as those aged more than 70 years.

Results: Of the 1163 patients treated with nivolumab, 416 were aged >70 years. Median age was 74 years (range, 71–82). Median overall survival (OS) was 17.8 months (95% CI 14.2–21.4). The median progression-free survival (PFS) was 3.4 months (95% CI 2.6–4.2). In the multivariate analysis, age >70 years was an independent risk factor for worse OS (HR: 1.57; 95% confidence interval (CI): 1.06–2.29; p = 0.027), steroid use at baseline (HR: 2.37; 95% CI: 1.44–3.74; p = 0.001) and LDH level >240 IU/L (HR: 1.63; 95% CI: 1.15–2.31; p = 0.007) were significantly associated with poor OS.

Conclusions: Results of this retrospective analysis confirm poor outcome in elderly NSCLC patients treated with nivolumab. Therefore, non-randomized studies are needed to determine the role of nivolumab in this patient group.

1163P Immunotherapy phase I trials in patients over 70 years with advanced solid tumours: The Gustave Roussy experience

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Background: More than half of new cases of cancer are diagnosed in patients over 65 years. However only few elderly patients have so far been included into trials, despite general awareness of the need. The revolution of immune checkpoint blocker development brings new hope in older patients because of clinical efficacy and low toxicity. Clinical indications are rising steadily but very few data are available in this population where co-morbidities, reduced functional reserve and immunosenescence may affect efficacy and tolerance.

Methods: All cases of patients enrolled in immunotherapy phase I trial between January 2012 and December 2016 in the Drug Development Department (DITEP) at Gustave Roussy were retrospectively reviewed. Case-control analysis was performed in a group of patients >70 years (elderly patients) to that of patients <70 years (younger patients) by trial and treatment dose. We compared cumulative incidence, grade and type of adverse events (AEs) and survival outcomes. Cumulative incidence was calculated according to Fine and Gray method and survivals using Kaplan-Meier method.

Results: The median age at the time of administration Nivo was 68 years. 135 patients were male, 157 patients had smoking history, 153 patients had a PS score of 0–1, and 23 patients received steroids. For all participants, median PFS was 2.9 months, over all response rate was 15.9% and disease control rate was 51.7%. In the multivariate analysis, PS score ≥2, steroid use at baseline, and LDH level >240 IU/L was significantly associated with poor PFS. Furthermore, in the multivariate analysis, PS score ≥2 (hazard ratio [HR]: 1.37; 95% confidence interval (CI): 1.86–2.29; p = 0.027), steroid use at baseline (HR: 2.37; 95% CI: 1.44–3.74; p = 0.001) and LDH level >240 IU/L (HR: 1.63; 95% CI: 1.15–2.31; p = 0.007) were significantly associated with poor PFS.

Conclusions: Results of this retrospective analysis confirm poor outcome in elderly NSCLC patients treated with nivolumab. Therefore, non-randomized studies are needed to determine the role of nivolumab in this patient group.

Legal entity responsible for the study: Gustave Roussy

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Background: Immunotherapy (IT) is now a standard of care in advanced NSCLC patients. However, patients may present with various patterns of response, including initial progression followed by long stabilization or response, making it difficult to decide whether or not we should continue the treatment at the occurrence of progression. Our aim was to explore the patterns of response based on CT-scans in order to differentiate real progression (PD) from pseudoprogression (PpsP).

Methods: We conducted a retrospective analysis of all NSCLC patients treated with IT in our Institution. All CT-scans were reviewed and the responses were assessed by RECIST 1.1 and IRECIST criteria. Seven different patterns of PD were considered based on the combination of target (T) and/or non-target (NT) and/or new lesions (NL). A confirmatory CT scan was performed at 4 weeks to discriminate real progression from PpsP. PpsP was defined as any decrease or stable disease for at least 6 months following an initial progression. Disassociated responses (DR) were defined as concomitant progressing and responding lesions for patients treated at least 6 months. Patterns of PD were correlated with overall survival (OS).

Results: Out of 202 patients treated by IT, 39 patients (19%) were excluded due to the absence of confirmatory CT. 87 patients (53%) had an initial PD, confirmed by a subsequent CT or, by death related to tumor progression. 14 patients (9%) experienced PpsP or DR. PpsP or DR had higher OS than PD patients (p < 0.05). The pattern which was the most likely to confer PsPD or DR was the appearance of NL in the thoracic area (lung, pleura) or lymph nodes. The concomitant increase of T, NT and appearance of NL was only observed in real PD. New extra-thoracic visceral lesions (especially liver and brain) were very unlikely to related to PpsP. New liver lesions occurring during IO were detrimental on OS (p = <0.05).

Conclusions: On the first occurrence of progression upon IT, a concomitant increase of T, NT and/or appearance of NL, especially extra-thoracic visceral lesions were strongly suggestive of real PD. IT should be stopped in these patients, and a confirmatory CT scan should be avoided.

Legal entity responsible for the study: Gustave Roussy

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Immune checkpoint inhibitors following targeted therapies in MITF family translocation renal cell carcinomas


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Background: MITF family tRCC is an aggressive disease with occasional responses to VEGFR inhibitors. Median PFS for patients under first ICI administered was 2.45 months (range, 0.05-40 months); among those, 4 patients experienced partial responses (17.4%) and 2 patients (9.5%) a stable disease with a median PFS of those responders under ICI of 9 months (range, 8.3-30), similar to the first line PFS with VEGFR inhibitors (9 months, range 1-29). One patient with partial response to Ipilimumab lasting for 9 months showed hyperprogressive disease following treatment by Nivolumab. With a median follow-up of 19 months, median OS was 23.5 months.

Conclusions: MITF family tRCC is an aggressive disease with occasional responses to ICI. Valid targets and clinical trials are warranted for this disease.

Legal entity responsible for the study: Pitit Salpetriere hospital

Funding: None

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Tumor flare reaction (TFR) in cancer treatments: a systematic review

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Background: In the last decade, TFR was described as a side-effect associated with immunomodulatory agents-DMOs (thalidomide and lenalidomide), and as a specific condition to chronic lymphocytic leukemia (CLL). However, this phenomenon is seen with the use of new immunotherapy (checkpoints inhibitors) in solid tumors, in addition, cases of TFR were reported in advanced gynecologic, prostate cancer and lymphoid malignancies. TFR is defined as an increase of lesion size related to treatment which simulates disease progression. This phenomenon that occurs after initiating cancer therapy is poorly understood and incidence is under-estimated, since not captured by RECIST. It has been suggested that TFR may be the result of immune system activation and may precede tumor shrinkage. TFR is associated with morbidity, severe cases were reported, some of them life-threatening or leading to death. So, early recognition and initial management of patients presenting with TFR, is critical.

Methods: From 1985 to 2016, a search was performed in the Pubmed, ASCO and ASH abstracts to identify publications reporting TFR or pseudoprogression.

Results: The incidence of all grades of TFR in CLL, ranged from 28% in a study in 58% in another trial. In CIL, painful lymph nodes and/or spleen enlargement were reported with a sudden onset after the first dose. Following initial progression (TFR), tumor response in patients treated beyond progression, was reported in melanoma trials 9.7% with ipilimumab, 10% with nivolumab, 6.7% and 12% with pembrolizumab, and in renal cell carcinoma 69% with nivolumab. Even if rare cases of life-threatening or fatal TFR were reported, symptoms are usually mild. While correct diagnosis and adequate management are critical, it is important to better recognize TFR, and avoid an effective treatment discontinuation. Some studies showed that treating patients beyond progression yielded tumor responses, considering TFR as predictive of response.

Conclusions: Treatment with immunomodulatory agents is associated with TFR. This is likely to be misinterpreted as progression, hence the need to identify appropriate clinical benefit criteria and the use of immune-related RECIST (iRECIST) in prospective trials for a better understanding.

Legal entity responsible for the study: Amina TALEB MD

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Melanoma brain metastases patients treated with stereotactic radiosurgery and ipilimumab versus stereotactic radiosurgery alone: a systematic review with meta-analysis

Results: We found 37 publications in our search and identified 4 retrospective studies comparing combined SRS and ipilimumab versus SRS only in MBM. The protocol was published in the PROSPERO register for systematic reviews. MEDLINE and CENTRAL databases were searched using PRISMA method by three separate reviewers. Studies that examined SRS and ipilimumab compared to SRS without ipilimumab in MBM were included. Newcastle-Ottawa Scale Risk of Bias Assessment and the GRADE evidence quality rating method were used for qualitative appraisal. Statistical analysis was performed using Review Manager.

Conclusions: Combining stereotactic radiosurgery and ipilimumab in melanoma brain metastases can dramatically improve survival rate compared to stereotactic radiosurgery without immunotherapy. There is no increased risk of radiation necrosis and/or intracranial bleeding with combining radiation and immunotherapy in our setting.

Legal entity responsible for the study: University of Central Florida College of Medicine

Disclosure: All authors have declared no conflicts of interest.

Conclusion: The use of RNAseq to orient patients to ICB is feasible. Estimation of immune infiltrate and function from RNAseq may be associated with treatment benefit either in term of PFS or in term of OS.

Clinical trial identification: MOSCATO (NCT01566019) and MATCH-R (NCT02517892)

Legal entity responsible for the study: Jean Charles Soria

Funding: None

Disclosure: L. Verlingue: Consultant for Adaptatherapy. J-C. Soria: Consultancy fees from AstraZeneca, Astex, Clovis, GSK, Gamnamabs, Lilly, MSD, Mission Therapeutics, Merus, Pfizer, Pharmamar Pierre Fabre, Roche-Genentech, SenoBiotech, Servier, Symphogen, Takeda. All other authors have declared no conflicts of interest.


Funding: None

Disclosure: All authors have declared no conflicts of interest.

Results: Median TMB was higher for tubular vs. non-tubular G (p = 0.032). Among the entire cohort, 3.3% and 7.4% of samples had a TMB > 20 and > 10, respectively. The proportion of tumors with TMB > 10 was greatest within tubular foreground structures (esophagus, stomach, duodenum, 11.2%). MSI was observed across all anatomic sub-types (range: 0.2–6.6%). Overall 1.2% of cases harbored receptor tyrosine kinase (RTK) fusions; colon and biliary tumors with RTK fusions had high (11) and low (2.5) median TMB, respectively. Validated immunoresponsive GA including PD-L1 amplification and POLE mutations were mutually exclusive and enriched in tubular GI structures (esophagus 0.5%, stomach (0.8%), colon (0.9%), duodenum (1.3%) and rectum (0.9%)). POLE mutation, but not PD-L1 amplification, correlated with high TMB (median 100 and 5.4, respectively). PIK3CA H1047R vs. E545K domain GA were strongly associated with response or resistance to ICPIs were compared to identify patient subsets for further study.

Methods: Comprehensive genomic profiling was used to determine TMB, microsatellite instability (MSI), and additional GA using previously described methods. GA were compared across those defined tumor subtypes and stratified by TMB status (mutations/DNA megabase), and those associated with response or resistance to ICPIs were compared to identify patient subsets.

Results: Median TMB was higher for tubular vs. non-tubular G (p = 0.032). Among the entire cohort, 3.3% and 7.4% of samples had a TMB > 20 and > 10, respectively. The proportion of tumors with TMB > 10 was greatest within tubular foreground structures (esophagus, stomach, duodenum, 11.2%). MSI was observed across all anatomic sub-types (range: 0.2–6.6%). Overall 1.2% of cases harbored receptor tyrosine kinase (RTK) fusions; colon and biliary tumors with RTK fusions had high (11) and low (2.5) median TMB, respectively. Validated immunoresponsive GA including PD-L1 amplification and POLE mutations were mutually exclusive and enriched in tubular GI structures (esophagus 0.5%, stomach (0.8%), colon (0.9%), duodenum (1.3%) and rectum (0.9%)). POLE mutation, but not PD-L1 amplification, correlated with high TMB (median 100 and 5.4, respectively). PIK3CA H1047R vs. helical (ES45SK) domain GA were strongly associated with high TMB (p < 0.0001), and similar findings were observed within MSI vs. MSS samples (p = 0.0001). Pre-existing GA that may decrease ICPI responsiveness including or JAK1 inactivating GA were rare (4.7% and 0.3% of cases, respectively). Representative clinical cases will be presented.

Conclusions: Inclusion of MSI-MSI and/or POLE to ICPIs were observed across GI cancers. Baseline genomic profiling may inform rational patient selection for immunotherapy treatment. The observation that high TMB and MSI are strongly enriched for PIK3CA H1047R, and whereas low TMB and MSS are enriched for ES45SK, warrants further study.

Legal entity responsible for the study: Samuel J. Klempner

Funding: None


Funding: None

Disclosure: All authors have declared no conflicts of interest.

Results: The proportion of tumors with TMB > 10 was greatest within tubular foreground structures (esophagus, stomach, duodenum, 11.2%). MSI was observed across all anatomic sub-types (range: 0.2–6.6%). Overall 1.2% of cases harbored receptor tyrosine kinase (RTK) fusions; colon and biliary tumors with RTK fusions had high (11) and low (2.5) median TMB, respectively. Validated immunoresponsive GA including PD-L1 amplification and POLE mutations were mutually exclusive and enriched in tubular GI structures (esophagus 0.5%, stomach (0.8%), colon (0.9%), duodenum (1.3%) and rectum (0.9%)). POLE mutation, but not PD-L1 amplification, correlated with high TMB (median 100 and 5.4, respectively). PIK3CA H1047R vs. helical (ES45SK) domain GA were strongly associated with high TMB (p < 0.0001), and similar findings were observed within MSI vs. MSS samples (p = 0.0001). Pre-existing GA that may decrease ICPI responsiveness including or JAK1 inactivating GA were rare (4.7% and 0.3% of cases, respectively). Representative clinical cases will be presented.

Conclusions: GA associated with increased sensitivity and/or resistance to ICPIs are observed across GI cancers. Baseline genomic profiling may inform rational patient selection for immunotherapy treatment. The observation that high TMB and MSI are strongly enriched for PIK3CA H1047R, and whereas low TMB and MSS are enriched for ES45SK, warrants further study.

Legal entity responsible for the study: Samuel J. Klempner

Funding: None


Funding: None

Disclosure: All authors have declared no conflicts of interest.

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Conclusions: GA associated with increased sensitivity and/or resistance to ICPIs are observed across GI cancers. Baseline genomic profiling may inform rational patient selection for immunotherapy treatment. The observation that high TMB and MSI are strongly enriched for PIK3CA H1047R, and whereas low TMB and MSS are enriched for ES45SK, warrants further study.

Legal entity responsible for the study: Samuel J. Klempner

Funding: None


Funding: None

Disclosure: All authors have declared no conflicts of interest.
Exceptional responses to ICPIs in POLE-mutated endometrial adenocarcinoma (EA), colorectal (CRC), and glialblastaoma (GBM) are described, but detailed pan-tumor POLE analyses are lacking.

Methods: We prospectively analyzed 80,853 primarily advanced solid tumors using hybrid-capture and comprehensive genomic profiling. TMB (mutations/Mb) was calculated from 1.11 Mb of sequenced DNA (PMID: 28420421). Known genomic alterations (IGAs) were defined as those reported as somatic in the COSMIC database or with published evidence indicating loss of function.

Results: POLE GA were identified in 5.0% of cases: melanoma (10%), duodenal adenoma (DA, 7.8%), uterus carcinosarcoma (CS, 6.9%), EA (6.4%), unknown primary carcinoma (UCP, 6.3%), NSCLC (6.1%), CRC (5.1%), prostate adenoma (5.0%), and GBM (4.6%). Most POLE GA were variants of unknown significance (VUS). POLE KGA were found in only 259 (0.3%) total cases, including ovari or uterus CS (1.2%), DA (1.3%), EA (1.2%), CRC (0.7%), GBM (0.6%), and UCP (0.6%). Patients with POLE KGA had a median age of 58 years (range 7–95); 33% were male. Median TMB in cases with POLE KGA, VUS and wild-type was 31.9 and 3.6, respectively (each p < 0.0001). Of cases with POLE KGA, 54% had high TMB (> 20), while 28% had low TMB (< 5). The most common SOI were R201C (6.7%), R141C (5.6%), and L183Q (4.4%). The most common parrental types may be less frequent than previously reported, particularly in advanced tumors. Identification of specific POLE GA associated with a hypermutated phenotype may be important to identify responders to ICPIs.

Legal entity responsible for the study: Foundation Medicine.

Funding: Foundation Medicine.


1171P Checkpoint inhibitors in MSI tumors: Lessons from a monocentric experience

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Background: Microsatellite unstable (MSI) tumors have shown high response rates to checkpoint inhibitors. Nonetheless, patterns of response and characteristics of responders remain poorly understood. We hereby report preliminary results of response to immunotherapy in a cohort of patients (pts) with metastatic MSI tumors.

Methods: We included all pts with metastatic MSI tumors of various histologic types treated at our institute with checkpoint inhibitors as monotherapy, or combinations. Somatic MSI status has been identified by immunohistochemistry with PCR at diagnosis and/or whole-exome sequencing in molecular screening trials at metastatic stage. Pts not previously known to have Lynch syndrome (LS) have been tested for inherited germline defect.

Results: From November 2014 through April 2017, 43 pts were enrolled. Main pts characteristics were as follow (median [range]): age at treatment was 56.4 years (26–78) and number of previous lines was 2 (1–3). The most frequently treated histologic types were gastro-intestinal (22/43: 51 colorectal (CRC), 2 small bowel, 2 biliary, 2 pancreatic, 1 duodenal) and gynecologic (11/43: 8 endometrial, 3 ovarian). Diagnosis of hereditary LS has been confirmed in 12 pts (28%), and screening results were as follow [median (range)]: age at treatment was 56.4 years (26–78) and number of previous lines was 2 (1–3).

Conclusions: We reported high response rates and survival benefit with checkpoint inhibitors in pts with MSI tumors remarkably in CRC and LS. A comprehensive analysis of immune microenvironment would be of clinical interest to characterize responders and non-responders.

Legal entity responsible for the study: Gustave Roussy Cancer Campus.

Funding: Gustave Roussy Cancer Campus.

Disclosure: All authors have declared no conflicts of interest.

1172P Single nucleotide polymorphisms in PD-L1 and outcome in nivolumab-treated advanced non-small-cell lung cancer patients


Respiratory Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan.

Background: Nivolumab is an established agent in the management of non-small-cell lung cancer (NSCLC); however, while some patients with lung cancer have marked responses to nivolumab, others do not respond. To determine the efficacy of nivolumab, we retrospectively evaluated treatment response with respect to PD-L1/PD-L1 SNPs among patients with NSCLC.

Methods: Between December 2015 and October 2016, a total of 68 patients with histologically or cytologically confirmed NSCLC were treated with nivolumab. Among these 68 patients, all of whom were registered at Kyoto University Hospital. Genomic DNA was extracted from peripheral blood and genotyping was performed using real-time PCR method. We investigated the possible correlation of PD-1/PD-L1 SNPs with PD-L1 expression in NSCLC patients treated with nivolumab.

Conclusions: The G/G and G/T genotypes of PD-L1 rs2282055 was significantly associated with better clinical response. The median PFS time was 4.2 months (95% confidence interval [CI], 1.7 months to 5.9 months) for the G/G and G/T genotypes of rs2282055 and 2.0 months (95% confidence interval [CI], 0.9 months to 2.2 months) for the T/T genotype (P = 0.0388). Moreover, the T/T and C/T genotypes of PD-L1 rs1411262 were significantly associated with better PFS in NSCLC patients treated with nivolumab.

Legal entity responsible for the study: Kyoto University.

Funding: None.

Disclosure: All authors have declared no conflicts of interest.

1173P Efficient identification of neoantigens for personalized cancer immunotherapy in advanced refractory epithelial cancer patients

F. Cheng, Z. Zou, J. Du, J. Wei, J. Shao, F. Meng, N. Dang, B. Liu

The Comprehensive Cancer Centre Of Drum Tower Hospital, Medical School of Nanjing University & Clinical Cancer Institute of Nanjing University, Nanjing, China.

Background: Recent genomic and bioinformatic technological advances have made it possible to dissect the immune response to personalized neoantigens encoded by tumor-specific mutations. However, rapid and efficient identification of neoantigens is still fraught with difficulty, and a systematic evaluation of personalized neoantigens-based immunotherapy in advanced refractory epithelial tumors is lacking.

Methods: Tumor and ctDNA samples from 16 advanced epithelial cancer patients were underwent mutational profiling by cancer-associated genes panel. Neoantigens identification were performed by two strategies: (1) As classic mode, somatic mutations were subjected to in silico analysis to predict potential high-affinity epitopes and mutated neoantigens screening in advanced epithelial cancer patients. Besides, targeted sequencing was identified. Approximately 10% neoantigen loaded DC vaccine and 10% bulk T cells were generated for personalized immunotherapy.

Results: Among the sequenced patients, 1−2 neoantigens recognized by autologous T cells have been successfully identified in 3 of 4 patients who utilized the classic mode and 6 of 12 patients who performed customized neoantigens library, respectively. Subsequently, a total number of 6 patients received immunotherapy targeting personalized neoantigen following immunomodulatory chemotherapy or radiotherapy. One patient with metastatic thymoma is achieving a complete and durable response beyond 12 months. In addition, immune related partial response was observed in another advanced pancreatic cancer patient. The remaining 4 patients achieved prolonged stabilization of disease with median PFS of 8.6 months.

Conclusions: Our customized neoantigens library can provide a novel approach for neoantigen-restricted advanced epithelial cancer patients. Besides, targeted sequencing is sufficient for somatic variant and neoantigen identification. The combination of two strategies can accelerate the neoantigen-based translational immunotherapy research into the paradigm of precision medicine.

Legal entity responsible for the study: Haorui Liu.
Results: Percentage of IC cells staining for PD-L1 varied from 6.54 to 10.18%, and TC from 5.46 to 15.85%, depending on the assay used (Table). For each assay, IC staining varied slightly to moderately between readers, with small non-significant differences between assays. Results for TC were comparable for all assays with significantly lower staining with SP142. For pairwise comparison revealed –0.3 to 1.6% differences in adjusted means between assays for IC, and for TC, –0.5 to 7.8% (SP142 vs other assays) and –1.9 to 2.7% (other comparisons). Retrospective allocation to binary cut-off (1%, 5% and 10%) for IC or TC only predominantly showed substantial or high Kappa agreement scores (0.6–0.8) for IC and TC between assays for each reader.

**Table: 1175P**

<table>
<thead>
<tr>
<th>Assay</th>
<th>PD-L1 on IC % (95% CI)</th>
<th>Reader ICC</th>
<th>PD-L1 on TC % (95% CI)</th>
<th>Reader ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>VENTANA SP142</td>
<td>8.18 (7.32–9.03)</td>
<td>0.699</td>
<td>5.46 (2.85–8.07)</td>
<td>0.609</td>
</tr>
<tr>
<td>VENTANA SP263</td>
<td>7.08 (6.22–7.94)</td>
<td>0.729</td>
<td>15.85 (13.24–18.47)</td>
<td>0.805</td>
</tr>
<tr>
<td>DAKO 22C3</td>
<td>6.54 (5.68–7.59)</td>
<td>0.532</td>
<td>13.19 (10.57–15.80)</td>
<td>0.883</td>
</tr>
<tr>
<td>DAKO 28-B</td>
<td>6.88 (6.02–7.74)</td>
<td>0.573</td>
<td>15.15 (12.54–17.77)</td>
<td>0.845</td>
</tr>
</tbody>
</table>

*Adjusted means for each assay; *Intra-class correlation per test between 5 readers

Conclusions: This is the first multicenter study for analytical comparison of PD-L1 IHC staining on IC and TC in UBC. High concordance rates across all assays were achieved between trained readers for scoring PD-L1 on IC and TC.

**Clinical trial identification:** ML39708

**Legal entity responsible for the study:** Roche Pharma AG

**Funding:** Roche Pharma AG

Disclosures: A. Hartmann: Membership of an advisory board: Roche, MSD, AstraZeneca Corporate-sponsored research: Novartis, Biontech, Illumina, Nanosting, Qiagen. G. Baretton: Membership of an advisory board Roche, Bristol-Myers Squibb, AstraZeneca Corporate-sponsored research Roche, Bristol-Myers Squibb. F. Lastocha: Membership of an advisory board: Roche NSCLC regional advisory board. Bristol-Myers Squibb NSCLC regional advisory board Corporate-sponsored research: Roche. R. Tauber: Membership of an advisory board: Roche, Sanofi, Bristol-Myers Squibb) Corporate-sponsored Research: conduct as subinvestigator of clinical trials. S. Heike-Schulz: Employee Roche Pharma AG. J. Ammann: Stock ownership: Roche Pharmaceuticals Other substantive relationships: Employee of Roche Pharma AG. W. Weichert: Conlicts of interest Advisory boards for Roche, AstraZeneca, MSD, Bristol-Myers Squibb, Pfizer, Novartis, Boehringer. Collaborative research with Roche, Novartis, AstraZeneca, Roche, Boehringer. All other authors have declared no conflicts of interest.
of 10%). CD8 (H-SCORE ≥ 284.4), FOXP3 (H-SCORE ≥ 155.4) and IOD-1 (H-SCORE ≥ 0.4) were significantly correlated with ORR and PFS. ORR was 77% in IOD-1 positive (n = 26), 32% in IOD-1 negative (n = 25) NSCLC pts. KRAS mutation, smoking status, and tumor location, response to platinum-based chemotherapy were not correlated with PFS and ORR. In multivariate analysis, positive PD-L1 and IOD-1 were the only factors correlated with ORR. ORR was 87.5% if both positive (n = 16), 60% if one of them was positive, 22.7% if both negative. Only IOD-1 was correlated with PFS.

Conclusions: Along with PD-L1, IOD-1 appears as a promising predictive factor for IO. A prospective validation is ongoing.

Legal entity responsible for the study: Sylvie Le Moullec

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1177P

Undiscovered immune heterogeneity in pancreatic adenocarcinoma (PDAC)

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Background: Our group previously identified three subtypes of human PDAC based on gene expression (PDAcassigner, classical, quasi-mesenchymal (QM) and exocrine-like subtypes). Recently Bailey et al. published four subtypes that were concordant with our three subtypes except that their immuno- genic subtype (enriched for immune genes) is a sub-type of the classical subtype. Here we applied our published prognostic/predictive colorectal cancer gene expression subtype classifier (CRGassocier) to PDAC patients to establish if these subtypes existed in PDAC and if they could be used to further refine our original PDAC subtypes.

Methods: CRGassocier signatures were used to classify 123 PDAC patient samples. Comparisons between different subtype classifications were performed using hypergeometric test. Patient survival analysis were performed using Kaplan-Meier plots and log-rank test. Pathway enrichment analysis was performed using gene set enrichment analysis (GSEA) on RNAseq expression profiles.

Results: We confirmed the existence of the five CRGassocier subtypes – enteroctye, goblet-like, inflammatory, stem-like and transit-amplifying (TA) - in PDAC. These subtypes were found to be sub-groups of original three PDAcassigner subtypes. By combining our subtype classification with Bailey et al.’s we classified PDAC into six subgroups: classical (pancreatic progenitors and immune- genomic), QM/quasiquamous (stem-like and inflammatory) and exocrine-like/ADEX (TA and enteroctye). Interestingly, we observed differences in the distribution of immune cells between Bailey’s immuno- genic and our inflammatory subtypes. We noted a sig- nificant increase in the expression of most of the immune regulatory genes in the infla- mmatory subtype (n = 7) compared to the immuno- genic subtype (n = 13).

Conclusions: This study further refines our published PDAC subtypes. The data reveals a new subgroups with a different immune and stromal profiles associated with different overall survival in this small data set. Further validation of these results is warranted to determine if subtype classifier can stratify patient samples for treatment with immunotherapy or immunotherapy combinations in PDAC.

Legal entity responsible for the study: The Institute of Cancer Research

Funding: National institute for health research

Disclosure: A. Scarpa: Associazione Italiana Ricerca Cancro (grant 12182) Fondazione Italiana Malattie Pancreas – Ministero Salute (CUP_J33G13000210001) European Community Grant FP7 Cam-Pac Cam-Pac Grant agreement no 602978 B.

Sadanandam: Entitled to a share of royalties received by the licensor for a patent owned with Merck, Illumina, and Regeneron All other authors have declared no conflicts of interest.

1178P

Optimized protocols to determine PD-L1 expression on tumor tissue and cytology samples from non-small cell lung cancer (NSCLC) patients using the 22C3 antibody with various Immunohistochemistry (IHC) autostainers

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Background: Pembrolizumab (pembro) is approved for treatment of PD-L1 expressing NSCLC in both treatment-naïve patients with a PD-L1 TPS ≥1%.

Methods: We retrospectively identified 33 patients diagnosed with HGSOC and treated with neoadjuvant platinum-paclitaxel from 2005-2014. Pre and post-neoadjuvant (NACT) on immune activation in stage IIIc/IV of high-grade serous ovarian carcinoma (HGSOC) and its relationship to treatment response.

Methods: We retrospectively identified 33 patients diagnosed with HGSOC and treated with neoadjuvant platinum-paclitaxel from 2005-2014. Pre and post-neoadjuvant treatment tissue samples were submitted to immunohistochemical analyses with anti-CD3, CD4 and CD8 antibodies for the identification of tumor-infiltrating lymphocytes (TILs). Pathological response classification to NACT was made according to Steffen Bosch (JCO 2015). Response score system (CRS) was explicitly defined (CRS-1; No or minimal tumor response, CRS-2; Appreciable tumor response amid viable tumor that is readily identifiable, CRS-3; Complete or near-complete response).

Results: The average age of patients was 63.44 years (66.90-75.00). The area under the ROC curve of post-surgery TILs for complete pathological response were: CD4 (epithelial): [0.73 (0.5; 0.79), p: 0.0084]; CD4 (stromal): [0.74 (0.51; 0.97), p: 0.0077] and CD8 (epithelial): [0.81 (0.63; 1.0), p: 0.02]. The expression of epithelial CD8 TILs in pre-surgery samples (≤ 5%) with neoadjuvant platinum was correlated with PFS (≤ 5% [OR: 0.10 (0.01; 1.19), p: 0.06]) and tumor response (≥ 25% [OR: 0.10 (0.01; 1.19), p: 0.06]). This finding was not significant in post-surgery samples (≤ 5% [OR: 0.34 (0.07; 1.64), p: 0.22]).

Conclusions: The high number of tumor-infiltrating lymphocytes in post-surgery samples was significantly associated with higher rates of complete pathological response and better prognosis. It is convenient to carry out further and multicentric studies to validate these results.

Legal entity responsible for the study: Hospital 12 de Octubre.

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1179P

Tumor-infiltrating lymphocytes expression in stage IIIc/IV of high-grade serous ovarian cancer: Variation with neoadjuvant chemotherapy and prognostic value

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Background: Ovarian cancer is a malignancy with a complex immune suppressive microenvironment mediated by the recruitment or induction of CD4+ regulatory T cell. The purpose of this study was to assess the effect of neoadjuvant chemotherapy (NACT) on immune activation in stage IIIc/IV of high-grade serous ovarian carcinoma (HGSOC), and its relationship to treatment response.

Methods: We retrospectively identified 33 patients diagnosed with HGSOC and treated with neoadjuvant platinum-paclitaxel from 2005-2014. Pre and post-neoadjuvant treatment tissue samples were submitted to immunohistochemical analyses with anti-CD3, CD4 and CD8 antibodies for the identification of tumor-infiltrating lymphocytes (TILs). Pathological response classification to NACT was made according to Steffen Bosch (JCO 2015). Response score system (CRS) was explicitly defined (CRS-1; No or minimal tumor response, CRS-2; Appreciable tumor response amid viable tumor that is readily identifiable, CRS-3; Complete or near-complete response).

Results: The average age of patients was 63.44 years (66.90-75.00). The area under the ROC curve of post-surgery TILs for complete pathological response were: CD4 (epithelial): [0.73 (0.5; 0.79), p: 0.0084]; CD4 (stromal): [0.74 (0.51; 0.97), p: 0.0077] and CD8 (epithelial): [0.81 (0.63; 1.0), p: 0.02]. The expression of epithelial CD8 TILs in pre-surgery samples (≤ 5%) with neoadjuvant platinum was correlated with PFS (≤ 5% [OR: 0.10 (0.01; 1.19), p: 0.06]) and tumor response (≥ 25% [OR: 0.10 (0.01; 1.19), p: 0.06]). This finding was not significant in post-surgery samples (≤ 5% [OR: 0.34 (0.07; 1.64), p: 0.22]).

Conclusions: The high number of tumor-infiltrating lymphocytes in post-surgery samples was significantly associated with higher rates of complete pathological response and better prognosis. It is convenient to carry out further and multicentric studies to validate these results.

Legal entity responsible for the study: Hospital 12 de Octubre.

Funding: None

Disclosure: All authors have declared no conflicts of interest.
1180P Development of OAT-1746, a novel arginase 1 and 2 inhibitor for cancer immunotherapy


Background: Clinical success of PD-1/PD-L1 and CTLA-4 checkpoint inhibitors demonstrated that resuscitation of anti-tumor immunity provides strong clinical benefits including curative responses. However, only a fraction of patients demonstrate long-lasting therapeutic effects prompting efforts to target additional pathways regulating antitumor immune response. Depletion of arginase inhibits proliferation and activation of T cells and is an important mechanism of immunosuppression. High plasma and tumor arginase (ARG) activity has been found in patients with a wide spectrum of cancers correlating with a poor prognosis. Therefore, we developed ARG inhibitors and report the immunoregulatory and antitumor activity of the lead compound (OAT-1746) alone or in combination.

Methods: The IC50 of the compounds was determined against the recombinant ARG1/3/2-M2 polarized, bone marrow derived macrophages and CHO cells transfected with human ARG1 were used to assess the cellular activity. Murine and human CD4+ CD8+ T cells were negatively isolated and incubated with anti-CD3/CD28 beads to trigger proliferation. CD3+ levels were measured. The in vivo antitumor efficacy was evaluated in syngeneic mouse models after oral administration at 50 mg/kg bid.

Results: We have developed potent, selective, orally active inhibitors of ARG1 and 2. Our lead compound, OAT-1746, has a low nanomolar activity against ARG1/2 and <50 nM cellular activity. It inversely arg1 arg 2 inhibited proliferation of human and murine T cells and restored CD3+ expression in ex vivo assays. In vivo, OAT-1746 showed good pharmacological properties with significant antitumor efficacy in multiple tumor models as a mono therapy and in combinations with checkpoint inhibitors and gemcitabine. The efficacy correlated with sustained PD effects: suppression of tumor arginase activity and 3.6-fold increase in plasma and tumor arginase concentrations that exceeded those required for the maximal stimulation of T cell proliferation. Induction of inflammatory markers in tumors confirmed reversal of immunosuppression. No toxicity was observed after multiple oral dosing in mono- or combinatorial therapies.

Conclusions: These results support the clinical development of OAT-1746 for cancer therapy.

Legal entity responsible for the study: OncoArendi Therapeutics SA

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Disclosure: All authors have declared no conflicts of interest.

1181P Pharmacokinetics (PK) and Pharmacodynamics (PD) of cergutuzumab amunaleukin (CA), a carconomeric antigen (CEA)-targeted interleukin 2 variant (IL2v) with abondidin to CD25

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Background: CA is a CEA-specific antibody fused to IL2v with abondidin to CD25. Compared to wildcard (w) IL-2, CA was designed to preferentially expand natural killer (NK) and CD8 T cells but not T regulatory cells (Tregs), to be retained within PBMCs and tumors. This data suggest that CA can be a potent combination partner for cancer immunotherapies targeting CEA+ solid tumors.

Clinical trial identification: NCT02492789

Legal entity responsible for the study: Incyte Europe Srl, Geneva, Switzerland

Funding: Incyte Europe Srl, Geneva, Switzerland


A first-in-human study of a novel monomucosal antibody INCSHR01210 directed against programmed cell death protein 1 (PD-1) in patients with advanced or metastatic cancer

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Background: INCSHR01210 is a novel PD-1 inhibitor with a safety and activity profile that may be different from that of other PD-1 inhibitors.

Methods: This is an ongoing, open-label, Phase1, dose-escalation/tumor-expansion study to evaluate the safety of INCSHR01210 in patients (pts) with relapsed/refractory solid tumors (NCT02492789). In Part 1, INCSHR01210 was administered IV in 3, 50% for up to 28 days. Of pts treated at the 200 mg Q4W flat dose; Part 2 data will be presented.

Results: As of data cutoff (3Feb2017), 23 pts were treated in Part 1 (median age, 62 y [range, 32–75]; 74% women). Treatment-related AEs in ≥20% of pts (all Gr3/4) were skin capillary hemangiomas and diarrhea (6%, 4%). Skin capillary hemangiomas were scattered and typically: <1 cm in diameter; on the face and upper chest; considered Gr1/2; regressed after stopping INCSHR01210. Immune-related AEs were consistent with other PD-1 inhibitors and observed in 3 (13%) pts. Treatment discontinuation due to AEs was reported in 1 pt (10 mg/kg; Gr1 skin hemangio- ma [resolved after stopping treatment]). The PK profile showed a dose-dependent increase in half-life from 3 days at 1 mg/kg to 7 days at 10 mg/kg. The receptor occupancy (RO) assessment at 10 mg/kg showed a target PD-1 inhibition of ~80% for up to 28 days. Of 21 efficacy evaluable pts, 5 (24%) had PR (median DOR, 163 days [range, 36–316]) and 19 (90%) had SD. SDs with PR included 1 pt each with SCC of the parotid gland (1 mg/kg), breast cancer (1 mg/kg), RCC (6 mg/kg), Melder cancer (10 mg/kg) and Kaposi’s sarcoma (10 mg/kg). Based on the safety (including tolerability of hemangiomas), PK and RO data from Part 1 and Part 2 at 600 mg Q4W flat dose, the remaining part of 2 patients were treated at the 200 mg Q4W flat dose; Part 2 data will be presented.

Conclusions: INCSHR01210 demonstrated manageable toxicity, but with Gr2/3 hemangio- ma not seen with prior PD-1 inhibitors. The recommended Phase 2 dose/schedule is 200 mg Q4W.

Clinical trial identification: NCT02492789

Legal entity responsible for the study: Incyte Europe Srl, Geneva, Switzerland

Funding: Incyte Europe Srl, Geneva, Switzerland

Background: PF-06801591 is a humanized IgG4 monoclonal antibody, blocks the Programmed Cell Death (PD-1) pathway by binding with high affinity to PD-1 and preventing its interaction with its ligands. A phase I study to assess the safety and tolerability of PF-06801591 after IV or SC administration is ongoing in patients (pts) with locally advanced or metastatic solid tumors.

Methods: PF-06801591 was administered at 0.015, 0.15, or 1.5 mg/kg IV once every 3 weeks (q3w), or 300 mg SC once every 4 weeks (q4w). Dose escalation occurred after the first 2-4 pts at each dose level were treated and then enrolled to each cohort for further PD assessment. Safety, tolerability, PK, and PD were assessed for all pts.

Results: As of January 31, 2017, 26 pts (ovarian cancer, n = 12; sarcoma, n = 6; head and neck cancer (SCCHN), n = 5; melanoma, n = 1; small cell lung cancer, n = 1; and malignant peritoneal neoplasm, n = 1) were treated in the dose-escalation phase: 0.5 (n = 2), 1 (n = 8), 3 (n = 7), 10 (n = 5) mg/kg IV, and 300 mg (n = 4) SC. Maximum tolerated dose was not reached. No drug-related SAEs or dose-limiting toxicities were observed. All drug-related AEs were Grade 1 or 2, and the most frequently reported (> 15% of pts include nausea (15.4%) and fatigue (15.4%). No dose-dependency of AEs was observed during IV dose escalation nor serious skin toxicity with SC administration. Four pts had partial response at 0.5, 1, and 10 mg/kg IV (ovarian pts) and 300 mg SC (SCCHN pt) and 3 pts had stable disease lasting >24 wks. There was a dose-dependent increase in the maximum concentration (Cmax) and area under the concentration-time curve (AUC) after IV administration. Following SC administration, PF-06801591 was slowly absorbed, with a median time to Cmax of 182 hrs. The mean average concentration (Cavg) after the first SC dose at 300 mg qiw was approximated 50% of Cmax following IV administration at 3 mg/kg q3w. Full receptor occupancy of PD-1 was seen in all dose cohorts.

Conclusions: Preliminary results demonstrate that PF-06801591 is well-tolerated with objective responses observed across the dose levels tested in both IV and SC forms. PK data confirmed the appropriateness of the dosing frequency.

Clinical trial identification: NCT02573259

Legal entity responsible for the study: Pfizer Inc.

Funding: Pfizer Inc.


NCT02715284

Legal entity responsible for the study: TESARO, Inc.

Funding: TESARO, Inc.

Clinical trial identification: ClinicalTrial.gov: NCT01438484
Legal entity responsible for the study: Cancer Research & Development, Phoenix, USA

Disclosure: All authors have declared no conflicts of interest.

Results: The patients were stratified by tumoral subtype and by CD8+ tumor-infiltrating lymphocytes (TIL) content. We observed a statistically significant effect on overall survival for the combination of 4SC-202 plus PD-1 (p = 0.04) and for the single agent 4SC-202 (p = 0.002). The combination was well tolerated.

Conclusions: The use of 4SC-202 in combination with PD-1 blockade offers a promising therapy for patients with advanced melanoma.

1192P 
Cytochalasin F and BFA inhibit long-term tumor cell proliferation but not primary tumor cells

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Background: A recent study showed that in vitro, CD8+ T cells can be expanded with minimal CD56+ contamination. Here we investigate if this can be achieved in vivo.

Methods: Mice were inoculated with syngeneic 4T1 tumor cells and treated with the following compounds: 1) Cytochalasin F; 2) BFA; 3) Control (PBS).

Results: Neoadjuvant treatment with Cytochalasin F and BFA inhibited long-term tumor growth in vivo whereas tumor proliferation was unaffected in vitro.

Conclusions: Cytochalasin F and BFA may be effective for tumor immunotherapy.

1189P 
4SC-202 plus anti-PD1: Breaking PD1-refractoriness to increase efficacy of checkpoint inhibition in patients with advanced melanoma

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Background: Despite successes in the treatment of melanoma patients with checkpoint inhibitors (CI), majority of patients do not respond to CI alone and a high unmet medical need remains for these patients. One promising approach to enhance the immuno-activity and alter the tumor microenvironment from an immune-deserted to an inflamed phenotype with combination therapy. Epigenetic modulation has been reported as one key determining factor in shaping the immune microenvironment and compounds altering these processes (e.g. histone deacetylases (HDAC) inhibitors) are particularly promising.

Methods: Tumor bearing animals (CT26 & C38 syngenic models) were treated with 4SC-202, an oral clinical stage combined HDAC class III (4SC-202) inhibitor, or CI PD-(L)-1 alone and in combination. Tumor growth was assessed continuously and after approx. 2 weeks of treatment tumors were excised and analyzed by flow cytometry and gene expression profiling. Additionally, animals not intended for these analyses were further monitored and tumor growth/survival was monitored.

Results: 4SC-202 treatment led to an increase of MHIC molecules and enhanced expression of inflammatory markers like IFN-γ and various chemokines in tumors. Detailed analysis of the tumors revealed that 4SC-202 strongly altered the immune cell composition; particularly the number of cytotoxic T cells (CTL) was markedly increased. Importantly, subsequent combination treatment of 4SC-202 with CIs in syngenic animal models showed a strong synergistic effect resulting in significant longer survival in both models leading to 55% of tumor free animals (C38 model).

Conclusions: In an ongoing study, patients with advanced melanoma who are refractory/non-responding to anti-PD-1 antibodies will be treated with 4SC-202 plus anti-PD1. These patients do not only represent a population with a high unmet medical need but melanoma also represents a model tumor for immunotherapy in general and CI in particular. We hypothesize that addition of 4SC-202 to anti-PD-1 antibody treatment may lead to increased immunogenicity of the tumor, an inflamed tumor micro-environment and ultimately to clinical benefit in anti-PD-1 refractory/non-responding advanced-stage melanoma patients.

Legal entity responsible for the study: 4SC AG

(irColitis) being amongst the most frequent ones. While the majority of patients with irColitis respond well when treated according to standard treatment algorithms with corticosteroids +/- other immunomodulatory drugs such as infliximab, some patients do not show resolution of diarrhea and colitis. In the present study, we analyzed the frequency of therapy-refractory irColitis, the underlying cause and useful diagnostic measures.

Methods: In this retrospective, monocenter study we collected data of 371 patients with metastatic and malignant melanoma patients had been treated with checkpoint inhibitor at the skin cancer unit center of the Department of Dermatology at the University Hospital Essen from 2006-2016. Demographic and clinical data of all patients were collected. Digital patient records of all 371 patients were searched for the terms “diarrhea” and “colitis”.

Results: We identified 41 patients with irColitis, the majority occurring during treatment with ipilimumab. Amongst these patients, 5 (12.2%) were refractory to standard immunomodulatory treatment with corticosteroids and infliximab. Therapy-refractory cases tended to show more severe inflammation in colonial biopsies performed during colonscopy (p = 0.04). CMV-DNA in colonial biopsies and in plasma pseudoplasms. In a phase 2 trial, its combination with paclitaxel improved overall survival (17.4m) vs paclitaxel (10.4m) in metastatic breast cancer (MBC) pts (HR 0.65, 80% CI 0.46-0.91, p = 0.1). Berstein et al. AACR2017). A pooled analysis was thus conducted to better characterize paclitaxel’s safety profile in combinations with paclitaxel.

Conclusions: This report on CMV reactivation during management of checkpoint inhibitor induced colitis emphasizes the need for repetitive diagnostic measures in treatment-refractory irColitis.

Legal entity responsible for the study: Ethics committee of the University Hospital Essen, University of Duessberg-Esen

Disclosure: All authors have declared no conflicts of interest.

1193P

Pooled data analysis of the safety and tolerability of intravenous pelareorep in combination with chemotherapy in 500 + cancer patients


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Background: Oncolytic viruses are promising cancer immunotherapies but questions have been raised regarding their safety. Pelareorep (REOLYSIN, R), an unmodified Reovirus Dearing strain, selectively replicates and lyses cancer cells and induces anti- tumor immunity. To date, 900+ patients (pts) have been treated with intravenous (IV) pelareorep. In a phase 2 trial, its combination with paclitaxel improved overall survival (17.4m) vs paclitaxel (10.4m) in metastatic breast cancer (MBC) pts (HR 0.65, 80% CI 0.46-0.91, p = 0.1). Berenstein et al. AACR2017). A pooled analysis was thus conducted to better characterize paclitaxel’s safety profile in combinations with paclitaxel.

Methods: 417 pts have been enrolled in 36 trials: 384 pts received IV pelareorep and 359 were in control arms. Data from 8 trials with paclitaxel (P), paclitaxel + pelareorep (PR), carboplatin + paclitaxel (CP) or carboplatin + pelareorep (CPR) were pooled. Standard doses of P (weekly) and CP were administered. Pelareorep IV dose was 3x1010 TCID50 (3-6 doses q21-28 d). Various advanced solid tumors were evaluated, including the 81 pts with MBC.

Results: A total of 363 pts were included in P (86), PR (95), CP (118) or CPR (264) groups. Median age (59-62 y) and ECOOG-0-1 status (90%-96%) were similar across the groups. All pts in P or PR had received prior chemo but only 26% in CP and 38% in CPR. Fatigue was the most common grade ≥3 treatment related adverse event (TRAE) in PR (9.5%) and CPR (8.9%) vs P (6.1%) and CP (2.9%). Grade ≥3 neutrophil count decreased and/or WBC decreased were more frequent in PR (15.8%/17.9%) than in P (5.8%/5.3%), but addition of pelareorep did not increase the frequency or severity of other grade ≥3 TRAEs with P or CP. Serious TRAEs (% of interest in P vs PR and CPR: included: fever (0 vs 3.2/0,8 vs 3.8), febrile neutropenia (0 vs 1.1/3.4 vs 3.4), sepsis (1.2/0 vs 0.8) and flu-like syndrome (0 vs 1.1 & 0 vs 0.8).

Conclusions: This is the largest database reported to date concerning the safety of an IV viral immune-stimulating agent in combination with paclitaxel or carboplatin-paclitaxel, is safe and well tolerated. Continued evaluation in a registration trial is warranted.

Clinical trial identification: NCI-US: NCI-GOG 1193P (NCT01193926). Ongoing, but not recruiting

Clinical trial identification: NCI-US: NCI-GOG 1193P (NCT01193926). Ongoing, but not recruiting

Disclosure: All authors have declared no conflicts of interest.

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Disclosure: A.A. Gutierrez: Chief Medical Officer and an employee of Oncolytics Biotech Inc. (or one of its affiliated corporations). Own shares in or have options to purchase shares in Oncolytics Biotech Inc. K. Cheetham: Employee of Oncolytics Biotech Inc. (or one of its affiliated corporations) and owns shares in or has options to purchase shares in Oncolytics Biotech Inc. M. Parsi, D. Galindez, L. O’Flynn: Paid consultant of Oncolytics Biotech. M. Caffey: President and CEO of Oncolytics Biotech Inc. As an employee of Oncolytics Biotech Inc. (or one of its affiliated corporations) he owns shares in or has options to purchase shares in Oncolytics Biotech Inc.

1194P Impact of prior immune checkpoint inhibitors on haematological toxicity in phase I patients receiving chemotherapy

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Background: Immune checkpoint inhibitors (ICIs) are used increasingly and earlier to treat multiple cancers. Although rates of on-treatment myelotoxicity are low, there are no published data on the long-term effects of ICIs. This is a pilot study to evaluate the impact of prior ICI exposure on chemotherapy-related myelotoxicity in patients in the Phase I setting.

Methods: We conducted a retrospective chart review of patients treated between 2012 and 2016 in the Drug Development Unit, The Royal Marsden Hospital. Multivariate logistic regression (including number of previous treatment lines and type of chemotherapy) was used to assess possible relationships between G3/4 neutropenia or thrombocytopenia and previous treatment with immunotherapy in patients receiving combination chemotherapy and targeted agents.

Results: We identified 99 patients (median age 62 years [range 34-79]; chemotherapy partners: cisplatin, carboplatin and paclitaxel). Fourteen patients (14%) received prior immunotherapy (PI) and 85 (86%) had no prior immunotherapy (NI). Patient characteristics, including baseline full blood count, previous pelvic radiotherapy, sites of metastasis and serum albumin, were comparable between the 2 groups, apart from number of previous treatment lines, which was lower in the PI patients (median 1.5 vs 2, p = 0.03). The odds of G4 neutropenia were higher in the PI group (OR = 7.1, 95% CI = 1.7-29.6, p = 0.007). PI was associated with significantly increased odds of G3/4 thrombocytopenia (OR = 14.4, 95% CI = 2.7-77.4, p = 0.002) on chemotherapy. In multivariate analysis, incorporating lines of prior chemotherapy (OR 1.3, 95% CI = 1.0-1.5, p = 0.037) and type of chemotherapy (carboplatin vs others: OR 2.3, 95% CI = 0.9-6.2, p = 0.094), the odds of developing G3/4 myelotoxicity were significantly higher in PI patients (OR 4.3, 95% CI 1.3-14.5, p = 0.02).

Conclusions: In our small cohort, previous treatment with immunotherapy was associated with the development of G3/4 myelotoxicity, especially thrombocytopenia, on subsequent chemotherapy. These preliminary data require further prospective validation but may impact on decision making regarding optimal sequencing of systemic therapy.

Legal entity responsible for the study: The Royal Marsden Hospital NHS Foundation Trust

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1195P Compromised efficacy of PD-L1 blockade therapy in axenic (germ-free) mice with syngeneic tumors

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Background: The microbiome can have profound effects on the innate immune system. Since the innate immune system regulates the adaptive immune response to antigens, we hypothesized that the microbiome may influence anti-tumor responses to immune checkpoint inhibitors. Accordingly, we sought to characterize the anti-tumor immunotherapies. See section of Clinical Trial Identification

Disclosure: A.A. Gutierrez: Chief Medical Officer and an employee of Oncolytics Biotech Inc. (or one of its affiliated corporations) and owns shares in or has options to purchase shares in Oncolytics Biotech Inc. K. Cheetham, A. Pennman, N. Noronha: Employee of Oncolytics Biotech Inc. (or one of its affiliated corporations) and owns shares in or has options to purchase shares in Oncolytics Biotech Inc. M. Parsi, D. Galindez, L. O’Flynn: Paid consultant of Oncolytics Biotech. M. Caffey: President and CEO of Oncolytics Biotech Inc. As an employee of Oncolytics Biotech Inc. (or one of its affiliated corporations) he owns shares in or has options to purchase shares in Oncolytics Biotech Inc.
effects of PD-L1 blockade therapy between mice with syngeneic tumors in conventional (specific pathogen-free, SPF) and germ-free (GF) environments.

**Methods:** B16-OVA or Lewis Lung Cancer (LLC) cell lines were injected subcutaneously into the flanks of 10–12-week-old C57BL/6 mice in both SPF and germ-free (axenic) environments. Mice with B16-OVA or LLC tumors in SPF (n = 6) and GF (n = 12, 6 females and 6 males) environments, and mice with LLC tumors in GF (n = 6) environments were randomized to receive the murine PD-L1 blocking antibody 10B5 or an isotype control. Tumor growth was evaluated every 2–3 days until days 35–40 when all mice were euthanized. Tumor size was compared between treatment groups in each environment at day 24 with the Mann Whitney U test. This project was approved by Mayo Clinic’s Institutional Review Board and Institutional Animal Care and Use Committee. Funding was provided by the NIH (K22 CA90628) and Mayo Clinic’s Center for Individualizing Medicine’s Microbiome Project.

**Results:** Under certain conditions, the anti-PD-L1 antibody 10B5 blocked tumor growth compared to an isotype control in SPF female mice with B16-OVA (p = 0.05), PD-L1 blockade had no effect on tumor growth in female axenic mice with B16-OVA (p = 0.20) or male axenic mice with B16-OVA (p = 0.34) or axenic mice with LLC (p = 0.56).

**Conclusions:** PD-L1 blockade therapy loses its anti-tumor efficacy in axenic mice. The microbiome may influence the efficacy of PD-L1 blockade through its effects on both innate and adaptive immune responses to tumors.

**Legal entity responsible for the study:** Aaron Mansfield at Mayo Clinic

**Funding:** National Institutes of Health; Mayo Clinic’s Center for Individualizing Medicine Microbiome Project.

**Disclosure:** All authors have declared no conflicts of interest.

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**1198P Immunomodulation by regorafenib alone and in combination with anti PD1 antibody on murine models of colorectal cancer**

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**Background:** Regorafenib is a small molecule inhibitor of multiple kinases involved in normal cellular functions and in pathologic processes such as oncogenesis, angiogenesis, and tumor immunity. Regorafenib is approved for the treatment of advanced colorectal cancer (CRC) and gastrointestinal stromal tumors. In addition, an overall survival benefit has recently been shown in patients with hepatocellular carcinoma who had previously progressed on sorafenib (RESOURCE trial). Immuono-immuno-oncology treatment strategies have recently expanded the arsenal of highly effective cancer therapies. In addition to their activity in monotherapy, they are being tested in combination with other therapies, including those inhibiting angiogenesis, to further improve their antitumor activity. We investigated the immunomodulatory effect of regorafenib alone and in combination with a mouse-reactive anti PD1 antibody in mouse models of CRC.

**Methods:** CT26 or MC38 syngeneic tumors were treated with regorafenib alone and in combination with anti PD1. We monitored tumor growth and analyzed the immune status of tumors ex vivo at the end of the study. Immune infiltrates were characterized by flow cytometry, intratumoral cytokines by multiplex ELISA, and expression of immunologically relevant genes by qPCR.

**Results:** Both regorafenib and anti PD1 inhibited the growth of MC38 tumors vs control, and this effect was significantly enhanced by concomitant treatment or when regorafenib was given after anti PD1. Regorafenib treatment most consistently reduced tumor-infiltrating macrophages in both MC3M and CT26 tumors in a dose-dependent manner. Additionally, signs of M1-type macrophage conversion were detected by elevated inducible NO synthase and reduced arginase expression. This may be due to a regorafenib-mediated inhibition of the CSF1 receptor, as shown in vitro in the murine macrophage cell line RAW264.7. Anti PD1 treatment was associated with elevated interferon-g levels, indicative of enhanced T cell activation.

**Conclusions:** These results warrant further exploration of a combination of regorafenib and PD1 for the treatment of colorectal cancer.

**Legal entity responsible for the study:** Bayer AG

**Funding:** Bayer AG

**Disclosure:** S. Hoff, S. Grünwald, L. Rose, D. Zopf; Employees of Bayer AG, and some are shareholders of Bayer AG stocks.

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**1199P Effect of MEK inhibition on PD-L1 and MHC-1 expression and on Cytokines production profile in NSCLC cells and in human lymphocytes**

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**Background:** Understanding of cancer-immune system interaction led to development of immunotherapy: anti-programmed cell death protein-1 (PD-1)-programmed cell death ligand-1 (PD-L1) antibodies are now used in non small cell lung cancer (NSCLC) treatment. MAPK cascade is a key intracellular network for tumor proliferation and recent data suggest that it is implicated in interplay of tumor and T~CD8~+~ CD69~+~ cytotoxic lymphocytes (CTL).

**Methods:** We evaluated PD-L1 mRNA level by Real Time qPCR (RT-qPCR) and its protein production, together with MAPK proteins, by western blot (WB), in NSCLC cell lines. Then, we studied the changes in PD-L1 and major histocompatibility complex class-I (MHC-I) expression and cytokines’ production, after MAPK-inhibition or stimulation, by MEK-inhibitor, cobimetinib, or phorbol 12-myristate 13-acetate (PMA), respectively. In addition, we explored the effect of cobimetinib on cytokines’ genes by RT-qPCR on cDNA, obtained from retro-transcription of RNA extracted from T-lymphocytes, derived from Peripheral blood mononuclear cells (PBMC) of healthy volunteers, by density gradient separation, and activated with anti CD3/anti-CD28-coated beads.

**Results:** WB and RT-qPCR for PD-L1 in NSCLC cells revealed a consistent correlation between mRNA and protein levels, together with activated MAPK and MEK1/2 signals, and suggested that ectopic PD-L1 mainly depends on transcriptional regulation. PD-L1 mRNA levels were significantly decreased by cobimetinib and increased by PMA, suggesting that MAPK can regulate PD-L1. Moreover, MEK inhibition resulted on cancer cells in increased synthesis of MHC-I, IFN-gamma, IL-6, IL-1b, and TNFalpha, involved in CTL activation, and on activated human phagocytic T-lymphocytes in increment of mRNA levels of IL-12, TNFalpha and IFNgamma, that are pro-inflammatory cytokines typical of CTL subset, that seems more involved in immune response against cancer.

**Conclusions:** These results demonstrate that MEK-inhibition induces the establishment of a pro-inflammatory microenvironment and may represent a potential mechanism to convert otherwise resistant cancers through treatment combination strategies of MEK-inhibitors and anti-PD-L1/PD-1 antibodies in NSCLC.

**Legal entity responsible for the study:** AO2 Università della Campania “Luigi Vanvitelli”

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**Disclosure:** All authors have declared no conflicts of interest.
**1203P** Exploring personalized immunotherapy opportunities in colorectal cancer

B. Navarro Rodriíguez,1 B. Bols BOTTOMLINE,2 P. Baumgartner,1 T. Nguyen-Ngo,1 P. Gannon,1 R. Genel,1 B. Stevenson,1 C. Sempoux,3 M. G. Sauvain, M. Hubner,4 D. Hahnel,1 P. Demoulié,1 C. Lonez,1 D. E. Gilham,2 Study design: To determine the future role of Immuno-RT in the rapidly evolving treatment paradigm of metastatic NSCLC and RCC.

Background: The irradiated tumor cell death can enhance antitumor immunity by increasing the diversity & quantity of tumoral antigen presentation, thereby augmenting anti-tumor immune response achieved with checkpoint inhibitors. The aim of this study was to assess the efficacy & toxicity of concurrent administration of nivolumab and radiotherapy.

Methods: We identified 6 patients that received concurrent nivolumab and radiotherapy to 19 lesions; metastatic NSCLC (n = 4), metastatic RCC (n = 2). Treatment-related toxicities were identified by retrospective review of patient notes. Enrollable lesions were assessed by RECIST 1.1 criteria. Pain score was used to assess symptomatic responses.

Results: Stereotactic and conformal radiotherapy were delivered to 9 and 10 lesions, respectively. Treatment sites (number of lesions): lung (n = 8), hip (n = 3), brain (n = 4), shoulder, scalp, ethmoid and adrenal. The median splitting radiotherapy & nivolumab did not exceed 2 weeks for all patients. No grade 3–4 toxicities were observed. Two of the lung cancer patients developed grade 1 pneumonitis. Fractionation schedules included 48 Gy in 4 fractions (4), 40 Gy in 4 (4), 25 Gy in 18 (30 Gy in 10), 25 Gy in 8 (20 Gy/4). Of the 14 measurable lesions, 86% had excellent response including complete response of 3 lesions. Symptomatic benefit was observed in 4 out of 6 treatment sites (66%).

Conclusions: The role of concurrent nivolumab & radiotherapy in patients with metastatic NSCLC and RCC has never been reported previously. In our study, concurrent administration of nivolumab and radiotherapy appears to be well tolerated with excellent radiological and symptomatic responses. Ongoing clinical trials may help define the future role of Immuno-RT in the rapidly evolving treatment paradigm of metastatic NSCLC and RCC management.

Legal entity responsible for the study: Javaher Ansari

Funding: None

Disclosure: J. Ansari: Paid honoraria for lectures and/or advisory boards for Amgen, AstraZeneca, Pfizer, Novartis, Boehringer Ingehe and Bristol-Myers Squibb, Roche and Sanofi. A. Shaukat: lecture fees and advisory board for Bristol-Myers Squibb. A. Alhamad: Advisory board for Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

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**1204P** Optimum fractionation of radiation dose to combine anti-PD-1 mAb in MC38 mouse model

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Background: The irradiated tumor cell death can enhance antitumor immunity by inducing antigen expression on tumor cells and activating lymphocytes. Radiotherapy (RT) combined with immunotherapy has revealed promising outcomes in various animal models. However, the optimum fractionation of radiation for priming immune response is controversial. This study aimed to explore the fractionation of radiation to maximize immunity in combinatorial treatment.

Methods: Mice bearing MC38 murine colon cancer were treated with up to 24Gy radiation given in various sized fractions as 2Gy x 11, 8Gy x 3, 8Gy x 1 followed by 2Gy x 8 and 2Gy x 12, and tumor growth followed. The immune response in the tumor, drainage lymph node (DLN) and spleen at 48h after radiation were assessed. 8Gy x 3 was chosen to combine anti-PD-1 immunotherapy. The abscopal effects and immune responses were assessed by flow cytometry and immunohistochemistry (IHC).

Conclusions: In these studies, a BT474-based CAR comprised of murine scFv fused to CD28-CD3ζ, signaling tail represented the best choice candidate after in vitro testing warranting further investigation. Subsequent studies will include in vivo xenograft models of colon cancer and neuroblastoma as well as target expression through immunohistochemistry assessing BT474 expression in a wide panel of tumor and normal tissues. This work focuses upon developing a package to support the clinical testing of BT474 targeted CAR T-cell therapy.

Legal entity responsible for the study: Celyad SA

Funding: Celyad SA


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**1204P** Concurrent immune-radiotherapy in lung and renal cancer - a new treatment paradigm

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Background: Concurrent administration of checkpoint inhibitors and radiotherapy (Immunno-RT) remains investigational and is the subject of multiple clinical trials. Nivolumab is an anti-programmed death-1 receptor monoclonal antibody that exerts checkpoint-mediated immune response against tumor cells. Nivolumab has received regulatory approval for the second-line management of metastatic non-small cell lung cancer (NSCLC) & renal cell carcinoma (RCC). Ionising radiation could increase the diversity & quantity of tumoral antigen presentation, thereby augmenting anti-tumor immune response achieved with checkpoint inhibitors. The aim of this study was to assess the efficacy & toxicity of concurrent administration of nivolumab and radiotherapy.

Methods: We identified 6 patients that received concurrent nivolumab and radiotherapy to 19 lesions; metastatic NSCLC (n = 4), metastatic RCC (n = 2). Treatment-related toxicities were identified by retrospective review of patient notes. Enrollable lesions were assessed by RECIST 1.1 criteria. Pain score was used to assess symptomatic responses.

Results: Stereotactic and conformal radiotherapy were delivered to 9 and 10 lesions, respectively. Treatment sites (number of lesions): lung (n = 8), hip (n = 3), brain (n = 4), shoulder, scalp, ethmoid and adrenal. The median splitting radiotherapy & nivolumab did not exceed 2 weeks for all patients. No grade 3–4 toxicities were observed. Two of the lung cancer patients developed grade 1 pneumonitis. Fractionation schedules included 48 Gy in 4 fractions (4), 40 Gy in 4 (4), 25 Gy in 18 (30 Gy in 10), 25 Gy in 8 (20 Gy/4). Of the 14 measurable lesions, 86% had excellent response including complete response of 3 lesions. Symptomatic benefit was observed in 4 out of 6 treatment sites (66%).

Conclusions: The role of concurrent nivolumab & radiotherapy in patients with metastatic NSCLC and RCC has never been reported previously. In our study, concurrent administration of nivolumab and radiotherapy appears to be well tolerated with excellent radiological and symptomatic responses. Ongoing clinical trials may help define the future role of Immuno-RT in the rapidly evolving treatment paradigm of metastatic NSCLC and RCC management.

Legal entity responsible for the study: Javaher Ansari

Funding: None

Disclosure: J. Ansari: Paid honoraria for lectures and/or advisory boards for Amgen, AstraZeneca, Pfizer, Novartis, Boehringer Ingehe and Bristol-Myers Squibb, Roche and Sanofi. A. Shaukat: lecture fees and advisory board for Bristol-Myers Squibb. A. Alhamad: Advisory board for Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

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**1200P** Functional screening of B7H6-based chimeric antigen receptor (CAR) designs


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Background: B7H6, a stress-induced ligand for the NK-activating receptor Nkp30, is widely expressed at the surface of transformed cells yet absent in healthy tissues. This makes B7H6 an attractive target for a CAR-T cell therapy with broad clinical applicability, including colon cancer and neuroblastoma. CARs are artificial receptors comprising an extracellular antigen-binding region (often a single chain variable fragment (scFv)) fused to an intracellular T-cell activation tail (usually CD3ζ). Here, we report the in vitro screening of various B7H6-based CAR designs differing by either the origin of their targeting moiety (murine versus humanized scFv), the costimulatory signaling module (either CD28 or 4-1BB), and the combination of CD28 and 4-1BB in a 3rd generation CAR context.

Methods: Primary human T-cell populations expressing the diverse B7H6-specific CAR constructs were compared for viability and fold expansion at the end of manufacturing as well as in vitro functionality (IFNγ secretion and cytotoxic activity when challenged with B7H6 expressing cell lines).

Results: All B7H6-based CAR T-cells yielded comparable fold expansion with high viability suggesting that the CAR design has no impact on process parameters. CARs targeting murine scFv origin were functionally superior to humanized versions in terms of killing and IFNγ release potentially due to a difference in target affinity between the scFv. Second generation CARs containing CD28 endowed CAR T-cells possessed superior in vitro anti-tumor activity compared to all other constructs. Cryopreservation of these 2nd generation CAR T-cells did not significantly reduce viability and potency post-thawing.
**Results:** Single dose of 24 Gy and 86 Gy x 3 through best tumor control. No abscopal effect was observed after radiotherapy alone. Fractionation of 86 Gy x 3 increased the irradiated tumor infiltrating lymphocytes (TILs). However, conventional 2 Gy doses decreased CD8+ TILs and CD8+ TILs and increased suppressor cell (MDSC) in spleen significantly. As the optimal fractionation to maximize tumor control, 86 Gy x 3 was chosen to combine anti-PD-1 mAb. Compared to radiotherapy or anti-PD-1 mAb alone, 86 Gy x 3 combining with anti-PD-1 mAb brought obvious abscopal effect. CD8+ T cells in the DLSs of the irradiated tumors were increased significantly in the combining group. Also, the combining treatment regimen increased CD8+ T cells and CD9+ T cells and decreased MDSC in the spleen. No serious toxicity of heart, liver, lung and kidney in each group was observed by using IHC.

**Conclusions:** Hypofractionation of 86 Gy x 3 was the fractionation of radiation dose to maximize immunity, compared to single dose of 24 Gy and conventional 2 Gy doses. Radiation with 86 Gy x 3 combining with anti-PD-1 mAb had synergistic anti-tumor effect.

**Legal entity responsible for the study:** Jinming Yu

**Funding:** None

**Disclosure:** All authors have declared no conflicts of interest.

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**1206P Efficacy of tumor treating fields (TTFields) and anti-PD-1 in non-small cell lung cancer (NSCLC) preclinical models**

M. Giladi, T. Voloshin, O. Taltyzhaki, U. Weinberg, E.D. Kirson

**Background:** Tumor Treating Fields (TTFields) are an effective anti-neoplastic treatment for chemotherapy-resistant malignancies. TTFields induce a cytotoxic effect on cancer cells by disrupting microtubules and septin filaments, which play key roles in mitosis. The mitotic effects of TTFields include abnormal chromosome segregation that triggers different forms of cell death. We evaluated TTFields’ effect on immunogenic cell death and its efficacy when combined with an immune checkpoint inhibitor (anti-PD1) in NSCLC.

**Methods:** Murine Lewis lung carcinoma (LLC) cells were treated with TTFields using the inoviko system. Levels of cell surface calreticulin (CRT) and intracellular ATP levels were evaluated using flow cytometry. High mobility group box 1 (HMGB1) secretion was measured using an ELISA assay. Mice inoculated with LLC cells were treated with isotype control, TTFields, anti-PD1, or TTFields + anti-PD1. Tumor volume monitoring and intra-tumor immune cell profiling were performed.

**Results:** TTFields induced elevated cell surface expression of CRT, decreased ATP levels, and promoted HMGB1 secretion. In vivo, the combined treatment of TTFields + anti-PD1 led to a significant decrease in tumor lung volume compared to all three other groups (P < 0.001). Significant increase in CD4+ tumor infiltrating cells was observed in the TTFields + anti-PD1-treated mice. Infiltrating cells demonstrated a significant upregulation of surface PD-L1 expression. Both F4/80+ CD11b+ cells and CD11c+ cells exhibited higher tumor infiltration and elevated PD-L1 expression, as compared to the control group. These findings indicate enhanced inflammatory antitumor environment conferred by the combination of TTFields + anti-PD1.

**Conclusions:** Our results demonstrate that TTFields treatment potentiates immunogenic cell death in NSCLC cancer cells. Combining TTFields with specific immunotherapies such as anti-PD-1 may enhance antitumor immunity and result in increased tumor control. In a phase III clinical study on TTFields in combination with either PD-1 directed mAbs, in patients with advanced melanoma, smoking-associated non-small cell lung carcinoma, or transitional cell carcinoma of the bladder who have received no more than one prior systemic treatment, NEO-PV-01 is custom designed and generated for each patient by DNA and RNA sequencing of a recently biopsied tumor, HLA typing, selection of neoantigen epitopes, and synthesis of up to 20 peptides (14-35 amino acids in length). Patients receive treatment with novelumab at a dose of 240 mg IV q2 weeks while their vaccine is produced. These peptides are formulated into four distinct pools, mixed with Poly-ICLC, and administered subcutaneously up to 4 non-rotating anatomical sites. Beginning at Week 12, patients receive five priming immunizations over a three-week period followed by booster vaccinations at Weeks 19 and 23 while continuing novelumab. The primary endpoint is safety. Secondary endpoints are ORR, CBR, PFS, and assessment of response conversion between Week 12 and Week 24.

**Exploratory endpoints include extensive immune monitoring. The study is open as of October 2016 with estimated enrollment of 90 patients.**

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**1207IP A phase II exploratory study of durvalumab (MEDI4736) in HIV-1 patients with advanced solid tumors**


**Background:** Durvalumab (MEDI4736) is a human monoclonal antibody (MAb) of the immunoglobulin G1 subclass that inhibits binding of programmed cell death ligand 1 (PD-L1) and its receptor, programmed cell death 1 (PD-1) to play an active and reversible role mediating T-cell exhaustion both in cancer and in chronic infections. Binding PD-1 to its ligand PD-L1 negatively regulates T-cell response, leading to an exhausted phenotype on CD8+ T-cells. Therefore, there is a potential of immunotherapeutic intervention targeting PD-1/PD-L1 in order to enhance anti-tumoral immune responses as well as to facilitate viral eradication. Durvalumab (MEDI4736) is a human monoclonal antibody (MAb) of the immunoglobulin G1 kappa (IgG1k) subclass that inhibits binding of programmed cell death ligand 1 (PD-L1) to programmed cell death 1 (PD-1; CD279) and CD80 (B7-1). Durvalumab has demonstrated in cancer patients a favorable safety profile with encouraging antitumor activity, but there are no data about tolerance or anti retroviral activity in HIV patients.

**Trial design:** This is an ongoing multicenter, open-label, phase 2 study (EUDRACT: 2016-004524-38) whose primary objective is to assess the feasibility of durvalumab at the recommended dose of 1500 mg every 4 weeks in HIV-infected patients with solid tumors for which no additional oncologic standard treatment is available. As secondary objectives the response rate (RECIST 1.1 and irRECIST), duration of response, PFS and OS will be measured. Exploratory objectives include the assessment of antiviral activity by measuring the changes in the HIV viral reservoir, the residual viral replication and the composition and function of circulating T lymphocytes and the study of molecular predictive factors of antitumoral activity on pretreatment tumor samples.

**Clinical trial identification:** EUDRACT: 2016-004524-38

**Legal entity responsible for the study:** Neon Therapeutics, Inc.
multiple solid and hematologic tumors deploying multiple mechanisms of action targeting tumor cells and cells from the neo-vasculature and tumor suppressive immune environment, resulting in an adaptive response. In our recently completed Phase 1 study in hematologic cancers, a single administration of autologous NKR-2 was safe with initial signs of clinical benefit. Likewise, to overcome the operational challenges, our trial design incorporates strategies to harmonize multiple clinical and manufacturing processes while also enhancing patient safety and clinical outcomes.

**Trial design:** THINK trial (Therapeutic ImmunoMunotherapy with NKR-2) is a EU/US open-label Phase I study to assess the safety and clinical activity of NKR-2 therapy administered in three infusions, two weeks apart in five solid tumor indications (CRC, urothelial, TNBC, pancreatic, ovarian) and two hematologic indications (AML/AH and MM). No lymphodepleting conditioning is required in this study. The study contains two consecutive segments. The dose escalation segment will enroll 18 patients in two separate hematologic and solid malignancy arms, and evaluate 3 dose levels of NKR-2 (3x10^6, 1x10^7 and 3x10^7 cells per injection) following a 1-3-3 design. The expansion segment will then enroll 96 additional patients in 7 separate cohorts for each indication with 3 steps of statistical analysis (overall futility, futility within each cohort and final evaluation). At time of submission, the trial has completed enrollment in its first cohort among solid indications.

**Clinical trial identification:** FDA: CYAD-NZT-002

**Legal entity responsible for the study:** CELYAD

**Funding:** CELYAD


**Background:** Focal Adhesion Kinase (FAK) is a pivotal intracellular mediator of extra-cellular contact interactions. It is over-expressed in cancer, with a long-established role in migration, invasion & survival, and is associated with poor prognosis. Recently FAK has been found to have a similar activity in recruitment of immunosuppressive cells to the tumour. We have shown that FAK inhibition can re-model the tumour immune microenvironment in vivo, shifting the balance from inhibitory Tregs, macrophages, fibroblasts and myeloid progenitors, to one which supports an active CD8+ adaptive immune response, resulting in tumour clearance and lasting immunity. FAK inhibition synergises with Programmed cell death receptor 1 (PD-1) blockade in more resistant models. Defactinib (VS-6863, Varotem) is a small molecule FAK inhibitor in Phase II development with an encouraging safety profile and biological activity.

Pembrolizumab (MK-3475, MSD) is a humanized IgG4/kappa monoclonal antibody to PD-1, licensed for the treatment of an increasing number of tumour types. This recently open trial will assess the safety, tolerability and preliminary activity of defactinib plus pembrolizumab in patients with advanced solid malignancies.

**Trial design:** FAK-PD1: a phase I/IIa clinical trial, combining 200 mg pembrolizumab as a 3-weekly IV infusion, with defactinib given orally twice daily at either 200 mg or 400 mg, before leading into three tumour-specific expansions (non-small cell lung cancer, mesothelioma and pancreatic cancer) at the selected dose. Up to 60 patients, PS 0-1, with adequate blood parameters, measurable disease, baseline tissue, and without contraindications to either agent, will be treated for up to 2 years until clear clinical progression, unacceptable toxicity, or withdrawal. Primary endpoint is safety (NCI-CTCAE v4.03); secondary endpoints include objective response rate (irRECIST), progression-free survival, FAK Y397 phosphorylation and immune cell infiltrate effects. Exploratory endpoints include comprehensive cellular and molecular characterisation of baseline and on-treatment tumour samples, and serial blood immune cell and cytokine profiling. Positive data will support further development of the combination.

**Clinical trial identification:** FAK-PD1 EudraCT number: 2015-003928-31

**Legal entity responsible for the study:** University of Glasgow & NHS Greater Glasgow and Clyde
PIVOT-02: A phase 1/2, open-label, multicenter, dose escalation and dose expansion study of NKTR-214 and nivolumab in patients with select, locally advanced or metastatic solid tumor malignancies

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Background: Abundance and functional quality of tumor infiltrating lymphocytes are positively linked with tumor response and improved survival with checkpoint inhibitors. NKTR-214 is a CD122-biased agonist that targets the IL2 pathway and is designed to provide sustained signaling through the heterodimeric IL2 receptor pathway (IL2R) to preferentially activate and expand NK and effector CD8+ T cells over CD4+ T regulatory cells within the tumor microenvironment. NKTR-214 has been administered to 28 patients with advanced cancers. NKTR-214 as a single agent demonstrated a substantial increase in both CD8+ T and NK cells within the tumor microenvironment in patients with prior immune checkpoint therapy (Bernatchez et al 2016). Given the favorable safety profile and strong biomarker data, a trial combining NKTR-214 and nivolumab was initiated.

Trial design: PIVOT-02 is a phase 1/2 open-label trial in patients (pts) with locally advanced or metastatic melanoma (mM), non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), urothelial carcinoma, or triple-negative breast cancer (TNBC). The primary objectives are to evaluate safety and tolerability, determine the recommended phase 2 dose (RP2D), and assess tumor response by RECIST 1.1. In an outpatient setting, NKTR-214 is administered at dose levels of 0.003, 0.006 and 0.009 mg/kg in combination with nivolumab at two flat dose schedules of either 240 mg q2w or 360 mg q4w. As of May 17, 17 pts (7 mM, 8 RCC, and 2 NSCLC) have been enrolled into 4 cohorts in the dose-escalation phase. In the dose-expansion phase, approximately 250 pts will be enrolled in five tumor types and eight indications; immunotherapy-naïve patients and patients who are relapsed/refractory to checkpoint therapy are being studied separately. Extensive blood and tissue samples are being collected to measure immune activation using immunophenotyping including flow cytometry, immunohistochemistry (IHC), T cell clonality and gene expression analyses. Enrollment is ongoing.

Clinical trial identification: NCT02983045

Legal entity responsible for the study: Nektar Therapeutics

Funding: Nektar Therapeutics

Disclosure: A. Diab: Consulting or Advisory Role – Celgene; CureVac; Nektar Research Funding - Celgene (Inst); Idera (Inst); Nektar (Inst); Pfizer (Inst) Travel, Accommodations, Expenses – Nektar. M.E. Hurwitz: Employment – Pfizer Consulting or Advisory Role – Nektar. N. Tannir: Honoraria - Bristol-Myers Squibb, Exelixis; GSK, Nektar; Novartis; Pfizer Advisory Role - Bristol-Myers Squibb; Exelixis, GSK; Nektar; Novartis Research Funding - Bristol-Myers Squibb; Epizyme; Exelixis; Novartis Travel - Bristol-Myers Squibb; Exelixis; GSK, Nektar; Novartis; Pfizer. C. Bernatchez: Employment – Lexicon (I) Stock - Lexicon (I) Advisory Role - Lion Biotechnologies Research Funding - Idera; Nektar Patents - Patent pending on ITLA as a marker for better CD8 T cells for adoptive immunotherapy. C. Haymaker: Cara L. Haymaker Research Funding - Idera; Nektar; B.D. Curti: Honoraria - Prometheus Speakers Bureau - Prometheus Research Funding - Bristol-Myers Squibb; Gilead Therapeutics; MedImmune, Prometheus; Viralytics Travel, Accommodations, Expenses – Agenox; MedImmune; Nektar; Prometheus, I. Gergel: Employment - Nektar Leadership - Corium International, Nektar Stock and Other Ownership Interests - Corium International; Nektar: M. Tagliaferri: Employment - Nektar Travel, Accommodations, Expenses - Nektar J. Zalevsky: Employment - Nektar U. Hoch, S. Aung, M. Imperiale: Employment - Nektar Stock and Other Ownership Interests - Nektar D. Cho: Honoraria - Bristol-Myers Squibb, Exelixis; Roche; Genentech Consulting or Advisory Role - Pfizer; Prometheus, S.S. Tykodi: Consulting or Advisory Role - Amgen; Prometheus Research Funding - Argos Therapeutics (Inst); Bristol-Myers Squibb (Inst); Exelixis (Inst); Genentech (Inst); GlaxoSmithKline (Inst); Prometheus (Inst). I. Puzanov: Consulting or Advisory Role - Amgen; Bristol-Myers Squibb; Roche; Genentech. H. Kluger: Honoraria - Merck Consulting or Advisory Role - Alexion Pharmaceuticals; Prometheus; Regeneron Research Funding - Merck (Inst) Travel, Accommodations, Expenses - Bristol-Myers Squibb P. Hwu: Stock and Other Ownership Interests - immatics; Lion Biotechnologies Consulting or Advisory Role - Lion Biotechnologies Research Funding - Bristol-Myers Squibb (Inst); Genentech (Inst). M. Sznol: Stock - Adaptive Bio; Amphivena; Intensity Thera Advisor - Adaptimmune; Alexion; Amgen; AstraZeneca; Biodexis; Bristol-Myers Squibb; Genentech; Immune Design; Janssen; Kyowa; Lilly; Lion Bios; Lyceara; MSD; Merus; Modulate; Nektar; Novartis; Pfizer; Symphogen; Theravance. All other authors have declared no conflicts of interest.
Clinical trial identification: NCT01844503 (006) NCT012721772 (006) NCT013927419 (069)

Legal entity responsible for the study: Bristol-Myers Squibb

Funding: Bristol-Myers Squibb

Diagnosis: C. Roberts: Served as a consultant for Amgen, Bristol-Myers Squibb, Merck, and Roche; received research funding from Amgen, Bristol-Myers Squibb, and Roche. J. Sadowska: Received consulting fees from Bristol-Myers Squibb, Merck Serono, MSD, and Novartis.

Table: 12130

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|------------------|------------------|------------------|
| NIVO+IPI (N = 409) | NIVO (N = 526) | IPI (N = 362) |
| Objective response rate (%) | 18.0 | 18.0 | 18.0 |
| CR, n (%) | 75 (18) | 83 (16) | 14 (4) |
| PR, n (%) | 166 (41) | 148 (28) | 51 (14) |
| Pts remaining in response (CR) | 63/75 (84%) | 75/83 (90%) | 11/14 (79%) |
| CR pts continuing on treatment | 17/75 (23%) | 41/83 (49%) | 4/14 (29%) |
| CR pts not continuing on treatment | 58/75 (77%) | 42/83 (51%) | 10/14 (71%) |

Conclusions: MEL pts treated with NIVO+IPI had a high rate of durable CRs, with the majority remaining in response and often not requiring additional treatment at a median follow-up of ~31 months. Some pts with a PR convert to a CR over time. Updated analyses based on 3-year data will be presented.

Clinical trial identification: NCT01844503 (006) NCT012721772 (006) NCT013927419 (069)

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Pfizers are 70%, 54%, and 50%, respectively. In treatment-naive pts, median PFS has not been reached; PFS rates at 6, 12, and 18 mo were 68%, 52%, and 52%. The most common (>19%) all-grade treatment-related AEs (TRAEs) were fatigue (39.1%), rash (32.8%), pruritus (26.6%), and arthralgia (15.6%). Grade 3 TRAEs were observed in 17.2% of pts (most common: lipase increased, n = 4; rash, n = 3; and anamia increased, n = 2). No treatment-related deaths occurred. Biomarker evaluation is ongoing.

Conclusions: Consistent with the phase 1 results, P F continues to be well tolerated and showed promising clinical activity. A phase 3 study in pts who are treatment-naive for advanced melanoma is ongoing (NCT02752074).

Clinical trial identification: NCT02178722

Legal entity responsible for the study: Incyte Corporation, Wilmington, DE

Funding: Incyte Corporation, Wilmington, DE; Merck & Co., Inc., Kenilworth, NJ

Disclosure: O. Hamid: Advisory Board - Merck & Co., Inc, Amgen, Novartis, Roche, Bristol-Myers Squibb; Corporate-sponsored Research - Incyte Corporation (Institution), Merck & Co., Inc. (Institution); Speaker’s Bureau – Bristol-Myers Squibb, Genentech, Novartis, Honoraria – Genetech, Bristol-Myers Squibb, Novartis. T.F. Gajewski: Advisory Board - Merck & Co., Inc; Corporate-sponsored Research - Incyte Corporation (Institution), Merck & Co., Inc. (Institution), T.M. Bauer: Corporate-sponsored Research - Incyte Corporation (Institution), Merck & Co., Inc. (Institution), A.J. Olszanski: Advisory Board - Merck & Co., Inc, Bristol-Myers Squibb; Corporate-sponsored Research - Incyte Corporation (Institution), Merck & Co., Inc. (Institution), Bristol-Myers Squibb, Novartis, Teva, Takeda, Pfizer; Other Substantive Relationships - Data Safety Monitoring Board: Takeda, J.J. Lake: Consult; Amgen, Array, AstraZeneca, BeneVir, Bristol-Myers Squibb, Castle, CheckMate, EMD Serono, Galaps, Novartis, Merck, Inst res suppy: ABBVir, Bostonbiomedcial, Bristol-Myers Squibb, Celllex, Corus, Delacth, Sprime, Genentech, immunocore, Incyte, Intensive, Medimmunity, Macrogenics, Novartis, pharmacies, Merck, Tesaro, A.S. Balanoumoukian: Corporate-sponsored Research - Medimmunity/AstraZeneca, Merck Serono, Genentech, Incyte Corporation (Institution), Merck & Co., Inc. (Institution), Other Substantive Relationships - Speaker’s Bureau at Bristol-Myers Squibb, Merck, Genentech, AstraZeneca; E.V. Schmidt: Employment and stock ownership at Merck & Co., Inc., B. Sharkey, J. Maleski, M.J. Jones: Employment and stock ownership at Incyte Corporation T.C. Gangadhar: Corporate-sponsored Research - Incyte Corporation (Institution), Merck & Co., Inc. (Institution), Bristol-Myers Squibb, Roche, Cereulan; Honoraria - Merck & Co., Inc., Novartis; Advisory Role - Bristol-Myers Squibb All other authors have declared no conflicts of interest.

1215O Results of COLUMBUS Part 2: A phase 3 trial of encorafenib (ENCO) plus binimetinib (BINI) versus ENCO in BRAF-mutant melanoma

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Background: The addition of a MEK inhibitor (MEK) to a BRAF inhibitor (BRAFi) in BRAFV600-mutant melanoma improves efficacy, including progression-free survival (PFS) and objective response rate (ORR), and attenuates some BRAFi-associated toxicities. Part 1 of the COLUMBUS study met its primary endpoint. The BRAFi ENCO 450 mg once daily (QD) + the MEKi BINI 45 mg twice daily (BID), COMBO300 improved PFS versus vemurafenib (VEM) alone and ENCO 300 mg QD (ENCO300) alone in patients (pts) with advanced BRAFV600-mutant melanoma. The tolerability of COMBO450 was favorable compared with VEM or ENCO300. In Part 2, the contribution of BINI to the combination was further evaluated by maintaining the same dose of ENCO in the combination (ENCO 300 mg QD + BINI 45 mg BID; COMBO300) and comparator arms (ENCO300 alone; ClinicalTrials.gov, NCT01909453; EudraCT, 2013-001176-38). 

Methods: Pts were randomized 3:1 to COMBO300 or ENCO300. Data from ENCO300 arms in Parts 1 + 2 were combined for the primary efficacy comparison of PFS by independent blinded central review (BCR). Other analyses included PFS for COMBO300 vs ENCO300 (Part 2 only), ORR, complete response (CR) and partial response (PR) by BCR and local review, and safety.

Results: Pt characteristics are presented in the Table. Median PFS (95% CI) for COMBO300 was 12.9 mo (10.1–14.0) vs 9.2 mo (7.4–11.0) for ENCO300 (Parts 1 + 2 and 7.4 mo (5.6–9.2) for ENCO300 (Part 2). The hazard ratio (HR) for COMBO300 vs ENCO300 was 0.77 (0.61–0.97; p = 0.029, 2-sided) vs ENCO300 (Parts 1 + 2) and 0.57 (0.41–0.78; P = 0.001, 2-sided) vs ENCO300 (Part 2). ORR, CR, and PR by BCR/local review (%) were 66/72, 81/1, and 56/62 for COMBO300, 30/56, 5/5, and 45/49 for ENCO300 (Parts 1 + 2), 50/55, 3/5, and 47/50 for ENCO300 (Part 2). Safety profiles were consistent with Part 1 (Table).

Conclusions: COMBO300 meaningfully improved PFS, ORR, and tolerability vs ENCO300, confirming the contribution of BINI to both efficacy and safety.

Clinical trial identification: Trial protocol number, CMEK162B3001 (release date, July 13, 2015)

Legal entity responsible for the study: Array BioPharma Inc

Funding: Array BioPharma Inc and Novartis Pharmaceuticals Corporation

Table: 1215O COLUMBUS Part 2: Baseline Characteristics, Duration of Exposure, and Safety

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<thead>
<tr>
<th>COMBO300</th>
<th>ENCO300</th>
<th>ENCO300 (Part 2) only</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>258</td>
<td>280</td>
</tr>
<tr>
<td>Patient characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline EOCG PS1, %</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>Baseline LDH high, %</td>
<td>31</td>
<td>28</td>
</tr>
<tr>
<td>Stage M1c disease at study entry, %</td>
<td>67</td>
<td>64</td>
</tr>
<tr>
<td>Tolerability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mediadosion of exposure, wk</td>
<td>52</td>
<td>32</td>
</tr>
<tr>
<td>AEs leading to discontinuation, %</td>
<td>12</td>
<td>13</td>
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<tr>
<td>AEs requiring dose modification, %</td>
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<td>AEs requiring additional therapy, %</td>
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<td>AEs (all grades ≥20% in any group), %</td>
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<tr>
<td>Vomiting</td>
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<td>Grade 3/4 AEs (≥5% in any group), %</td>
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<tr>
<td>Increased alinineaminotransferase</td>
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Funding: Array BioPharma Inc and Novartis Pharmaceuticals Corporation

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Disclosure: R. Dunner: Honoraria from and consulting/advisory role for Roche, Bristol-Myers Squibb, GSK, MSD, and Novartis; research funding from Roche, Bristol-Myers Squibb, GSK, MSD, and Novartis. P.A. Ascenso: Consulting fees from Bristol-Myers Squibb, Roche, Genentech, MSD, Ventana, Novartis, Amgen, and Array BioPharma; research funding from Bristol-Myers Squibb, Roche, Genentech, Ventana, and Array BioPharma. H. Gogas: Consultant for Roche, Bristol-Myers Squibb, MSD, Novartis, and Agen. A. Arance: Honoraria from and consulting/advisory role and travel expenses from Roche and Bristol-Myers Squibb. M. Mandala: Honoraria from Novartis, GSK, Bristol-Myers Squibb, MSD, and Roche; speakers bureau for Novartis, GSK, Roche, and Bristol-Myers Squibb; advisory board member for Novartis, Amgen, MSD, and Bristol-Myers Squibb; research funding from Roche. C. Garbe: Honoraria and travel expenses from and served in a consulting/advisory role and speakers bureau member for Amgen, Bristol-Myers Squibb, MSD, Novartis, Roche, and Philogen; research funding for University Hospital Tübingen from Bristol-Myers Squibb, Novartis, and Roche. D. Schadendorf: Honoraria and travel expenses from and consulting/advisory role and speakers bureau for Amgen, Bristol-Myers Squibb, Novartis, Roche, and MSD; research funding for University Hospital Essen from Amgen, Bristol-Myers Squibb, Roche, Novartis, and MSD. I. Krasiová: Advisory board member for Bristol-Myers Squibb, Novartis, Roche, MSD; travel expenses from Bristol-Myers Squibb and MSD. R. Gutzmer: Consulting fees and/or honoraria from Roche, Bristol-Myers Squibb, MSD, GSK, Novartis, Almirall, Leo, Amgen, Pfizer, Merck Serono, Boehringer Ingelheim; research funding from Roche, Novartis, Pfizer, Pierre Fabre, Johnson & Johnson; travel expenses from Roche, Bristol-Myers Squibb, Roche. V. Chiorion-Silén: Honoraria received from Novartis, GSK, Bristol-Myers Squibb, MSD, and Roche; speakers bureau for Novartis, GSK, Roche, and Bristol-Myers Squibb; advisory board member for Novartis, Amgen, MSD, Bristol-Myers Squibb, and Roche. J. W. de Groot: Consulting/advisory role for Amgen, Bayer, Celgene, Roche, Bristol-Myers Squibb, GSK, MSD, and Merck Serono. N. Yamazaki: Advisory role for Chugai Pharma, Bristol-Myers Squibb Japan, and Ono Pharmaceutical; honoraria from Chugai Pharma, Bristol-Myers Squibb Japan, Ono Pharmaceutical, GlaxoSmithKline, Takeda, AstaZeneca, Japan, Boehringer Ingelheim, and Maruho. C. Loquai: Advisory board member for Roche, Novartis, Bristol-Myers Squibb, BioNTech, General Health, and Amgen; speakers bureau from Roche, Novartis, B Bristol-Myers Squibb MS, and MSD; travel expenses from Roche, Novartis, Bristol-Myers Squibb, MSD, and Amgen. L. A. de Parseval: Employee of Novartis Pharma AG; may own stock or stock options. M. Pickard: Employee of Array BioPharma; may own stock or stock options. V. Vanderschueren: Employee/advisory role at Array BioPharma; stock or other ownership of Array BioPharma and Incyte Corp. C. Robert: Consultant for Roche, Novartis, Bristol-Myers Squibb, MSD, and Agen. K. T. Flaherty: Honoraria from and consulting/advisory role for Novartis and Array BioPharma; research funding from Novartis. All other authors have declared no conflicts of interest.

Results:

Of the 15 pts enrolled, 10 (66.7%) had PD-L1 staining (≥1%) and 5 (33.3%) had ≥5% PD-L1 staining. 1 pt had EOCG PS 0/1, and 1 (6.7%) had stable brain metastases. Median follow-up was 19.7 mo (range, 15.9-31.1). 3/15 (20.0%) pts had DLTs (1 pt had grade 4 neutropenia; pt 2 had grade 4 ALT increase; and pt 3 had grade 4 ALT, grade 3 AST, and grade 3 GGT increase); all resolved. Thus, this dose was the MTD and recommended ph 2 regimen. 430 pts had confirmed or unconfirmed PD. Of the 430 pts, 67% had 1 pt had CR, 9 had PR; an additional 2 pts had SD and 3 had PD. ORR (RECIST v 1.1, investigator; confirmed only) was 59%; 8 pts had PR; an additional 3 pts had SD and 4 had PD. Median time to response was 2.8 mo (range, 2.2-30.0); median DOR was not reached (range, 2.8-26.5 mo). Among the 8 pts with confirmed ORR, 6 had ongoing responses and 2 had progression at data cutoff. 2 pts remained on triplet therapy, 2-d D + T, and 4 pts pembrolizumab D + T as of last follow-up.

Conclusions: Updated results show that approved doses of pembrolizumab + D + T continue to demonstrate promising antitumor activity for BRAF-mutant melanoma. A randomized ph 2 study is currently evaluating this triplet regimen as first-line therapy for BRAF-mutant melanoma.

Clinical trial identification: NCT02130466, May 1, 2014

Legal entity responsible for the study: Merck & Co., Inc., Kenilworth, NJ, USA

Funding: Merck & Co., Inc., Kenilworth, NJ, USA

Disclosures: A. Ribas: Stock ownership with Kite Pharma; honoraria with Amgen, Pfizer, Roche, and Merck F. S. Hodi: Advisory board member with Merck, Genentech, Novartis, EMD Serono, and Amgen; research funding from Bristol-Myers Squibb. V. Atanasov: Advisory board member with Bristol-Myers Squibb, MSD, Pfizer, Roche, and Novartis; research funding from GSK; travel expenses from Novartis. D. Atkins: Honoraria from Bristol-Myers Squibb, Roche, AstraZeneca, and Merck; research funding from Array BioPharma; travel expenses from Sanoz BioPharma; research funding from Bristol-Myers Squibb and Roche.

Background: Metastatic melanoma (MM) is widely treated with both kinase inhibitors and immunotherapies, providing meaningful survival benefit. Contrasting CGP and TMB results across MM subtypes provides a blueprint for rational decision making in light of increasing effective therapeutic options.

Methods: CGP for 2,225 MM evaluated up to 315 genes plus introns of 28 genes comprised 1.1 Mb of sequenced DNA. Base substitutions, insertions and deletions (short variants; SV); rearrangements; and copy number changes were assessed.

Results: We evaluated 9 MM subtypes: routine cutaneous (CT), desmoplastic (DM), acral lentiginous (AL), Spitzoid (SP), gynecologic mucosal (GMC), head and neck mucosal (HN), anorectal (ARM) and ocular (OC). Each group harbored characteristic genomic alterations (GA). BRAF was mutated in 36% of CT (92% SV; 8% amplifications, fusions or cases with >1 BRAF GA). Patients with TMB ≥20 mut/Mb were common in CT and DM, but ≤5% in all other subtypes. The frequency of BRAF GA was lower in AL, GMC, HN, ARM and OC, PF, cutaneous and anorectal fusions in BRAF (60%) and other kinases. KIT GA were prominent in GMC and AL. Key findings include novel driver of BRAF inhibitor resistance including BRAF rearrangements, kinase duplications and MEK GA.

Conclusions: In the largest cohort of MM with CGP to date, genomic profiles and immunotherapies, providing meaningful survival benefit. Contrasting CGP and TMB results across MM subtypes provides a blueprint for rational decision making in light of increasing effective therapeutic options.

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Table: 1217PD

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<th>CT</th>
<th>DM</th>
<th>AL</th>
<th>SP</th>
<th>GMIC</th>
<th>HN</th>
<th>ARM</th>
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<td>12</td>
<td>22</td>
<td>22</td>
<td>60%</td>
<td>22</td>
<td>7</td>
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<tr>
<td>BRAF GA</td>
<td>38%</td>
<td>0%</td>
<td>18%</td>
<td>18%</td>
<td>15%</td>
<td>13%</td>
<td>2%</td>
<td></td>
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<tr>
<td>Other driver GA</td>
<td></td>
<td></td>
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<td>Fusions in:</td>
<td></td>
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</tr>
</tbody>
</table>
| NFI (21%)        |      |    |    |    | NFI (32%) | NFI (18%) | NFI (43%) | NFI (18%)
| (12%) PTEN       |      |    |    |    | (18%) PTEN | (9%) EGFR | (14%) BRCA2 | (14%)
| NFI (30%)        |      |    |    |    | PTEN (13%) | NTRK1 (5%) | NTRK1 (14%) |    |
| TMB ≥10 mut/Mb   | 61%  | 92%| NA | NA | 5%   | 5% | 14% | 3%
| TMB ≥20 mut/Mb   | 42%  | 83%| NA | NA | 0    | 5% | 0%  | 1% |

1218PD

Precision medicine for the treatment of metastatic uveal melanoma: A pilot study


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Background: There is no standard active treatment for metastatic uveal melanoma. Precision medicine with high-throughput genomics could improve the outcome of patients suffering of “hard-to-treat” cancer.

Methods: Metastatic uveal melanoma included in the prospective TREAT20Plus study had fresh tumor biopsies that were subjected to a complete genomic analysis program (WGS, whole exome seq, RNAseq, Methylome, Proteome and cell culture). Integrative had fresh tumor biopsies that were subjected to a complete genomic analysis program (WGS, whole exome seq, RNAseq, Methylome, Proteome and cell culture). Integrative

Results: Thirteen patients (6 F, 7 M) were biopsied. Age: 68 (33-81). Site of biopsy: soft tissue: 5, liver: 4, lung: 2, pleura: 1, lymph node: 1. Pre-treatment number: 2 (0-4) and type iv chemotherapy: 10, checkpoint Inh, intra-hepatocutaneous. Genomic results were available in the first 10 patients within 34 days (31-40). The number of mutations was low median: 25 (16-44). Mutations were found in GNAQ (11), GNA11 (6), BAP1; 3, SFR1; 4. We detected one gene-fusion: ZNF704-PKIA. The most frequent gene overexpression affected the following genes: MYC, 7, MET, 5, BCL2, 4, CCND2, 1, ERBB3, 1. There was a loss of expression of CDKN2A: 2, PTEN: 1, EFS: 1. A slightly up-regulated expression of ALK was detected in one patient and confirmed as an oncogenic, ALK44 isoform that originates from an alternative intranuclear transcription site start in 19. At time of recurrence a second biopsy showed a complete loss of CDKN2A expression through a bi-allelic loss of chromosome 9. Treatment recommendations were the following: inhibitor of MEK: 10, of MET: 5, of CDK4/6: 4, of ALK: 1, of PI3K: 1. Treatment was initiated in 7 patients: 5 received trametinib, one patient each received palbociclib, crizotinib or cabozantinib, respectively. Among the 6 currently evaluable patients one showed minor response (15%), one a stable disease, one progressive disease, and 3 patients cannot yet be evaluated.

Conclusions: Genomic integrative analysis showed a net advantage over exome-only or panel sequencing. This strategy is clinically feasible and led to individualized treatment recommendations. Treatment outcome will be presented for the whole cohort.

Legal entity responsible for the study: Charite Comprehensive Cancer Center

Funding: German Federal Ministry of Research and Education (BMBF) grant Nr. 031A512 Max Planck Society

Disclosure: M. Schuetze, C. Wierling, B. Lange: Employees of Alacris Theranostics. T. Kessler: Employee of Alacris Theranostics. V. Keilholz: Employee and owns stock in Foundation Medicine. All other authors have declared no conflicts of interest.

1219PD

Combined radiofrequency ablation and ipilimumab in uveal melanoma: Results from the SECIRIA-UUM trial

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Medical Oncology Department, Het Nederlands Kanker Instituut Antoni van Leeuwenhoek (NKI-AVL), Amsterdam, Netherlands, Department of Biometrics, Het Nederlands Kanker Instituut Antoni van Leeuwenhoek (NKI-AVL), Amsterdam, Netherlands, Department of Pathology, Het Nederlands Kanker Instituut Antoni van Leeuwenhoek (NKI-AVL), Amsterdam, Netherlands, Core Facility Molecular Pathology & Biotanking, Het Nederlands Kanker Instituut Antoni van Leeuwenhoek (NKI-AVL), Amsterdam, Netherlands, Department of Clinical Oncology, LUMC, Leiden, Netherlands

Background: After enucleation or radiotherapy of the primary lesion, 50% of uveal melanoma (UM) patients develop distant metastases. In contrast to cutaneous melanoma, targeted therapies and checkpoint inhibitors failed to improve overall survival (OS) in UM. Chemenoembolization or intrahepatic artery perfusion improved local control, but failed to show OS benefit. The anti-CITL-4 antibody pralsetam (IPI), showed limited clinical activity in UM, thus combination therapies may be required. Preclinical experiments in a murine melanoma model indicated that additional radiofrequency ablation (RFA) enhanced antigen presentation and induced durable responses.

Methods: We therefore have set up a phase Ib/2 study to assess safety and efficacy of the combination of RFA and IPI in UM patients with at least 2 unresectable liver lesions. In the phase Ib part patients underwent RFA of one liver lesion and received 4 courses IPI 0.3mg/kg, 1mg/kg or 10mg/kg qweekly in a 3 + 3 design. Primary endpoint of the phase Ib part was safety in terms of dose limiting toxicities per cohort to define the recommended phase 2 dose (RP2D). Primary endpoints of the phase 2 part were confirmed objective response rate (ORR) and disease control rate (DCR) according to RECIST 1.1 (only non-RFA lesions), secondary endpoints were progression free survival (PFS) and OS.

Results: IPI 10mg/kg + RFA was defined as the RP2D. After 19 patients had been treated, the study was amended to adjust the RP2D to IPI 3mg/kg + RFA, because 9 patients (47%) had developed grade 3 colitis. In the 3mg/kg IPI + RFA cohort also 19 patients have been treated, and balanced characteristics were balanced between the cohorts. Treatment related grade ≥3 AEs were seen in 53% of patients in the 10mg/kg cohort versus 32% in the 3mg/kg cohort. No confirmed objective responses were observed, the confirmed DCR was 21% in the 10mg/kg cohort and 11% in the 3mg/kg cohort. Median PFS was 2.8 months and was comparable for both groups, median OS was 13.6 months for the 10mg/kg cohort versus 9.5 months for the 3mg/kg cohort (p = 0.23).

Conclusions: The combination of IPI 3mg/kg + RFA was safe but showed limited clinical activity in UM. However, overall survival seems to be longer compared to other study cohorts of UM patients, especially in the IPI 10mg/kg cohort.

Clinical trial identification: EudraCT Number: 2011-004200-38

Legal entity responsible for the study: NKI-AVL

Funding: Bristol-Myers Squibb

Disclosure: J.V. Thienen: Advisory board: MSD, Bristol-Myers Squibb. B.A. van der Vehet: Advisory role: Bristol-Myers Squibb, MSD, Pfizer, Roche, Novartis, NeoTherapeutics Research grants: Bristol-Myers Squibb, MSD, GSK, C.U. Blank: Advisory board: Bristol-Myers Squibb, MSD, Novartis, GSK, Pfizer, Lilly. Roche Research grant: Bristol-Myers Squibb, Novartis. All other authors have declared no conflicts of interest.
Phase 2 study of neoadjuvant dabrafenib + trametinib (D+T) for resectable stage III(B/C) BRAF V600 mutant melanoma


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Background: Combination D+T improves the overall survival (OS) of patients (pts) with BRAF V600 mutant advanced melanoma, and an adjuvant trial is in progress (NCT01682083). We sought to explore neoadjuvant D+T for pts with bulky but resectable stage III melanoma.

Methods: In this phase 2 study, 35 pts received standard dose D+T for 12 wks prior to complete resection of the pre-therapy tumour bed (RES), then 40 wks of further D+T. Eligible pts had ECOG PS ≤ 1 with histologically confirmed resectable bulky AJCC v7 stage III(B/C) BRAF V600 mutant melanoma. CT and PET scans were performed at baseline and 12 wks just prior to RES for RECIST and metabolic complete response (cR and mCR respectively). CT monitoring was continued 12 wks thereafter to 2 yrs then 6 moly thereafter until 3 yr post-op. CD8+ T cell count at baseline and by week 1. The primary endpoint was the complete pathological response (pCR) and RECIST response rate (RR) at wk 12. Secondary endpoints were surgical morbidity, mCR, relapse free survival (RFS), OS, toxicity and translational endpoints.

Results: At data cut 18 April 2017, 35 pts had commenced D+T. 33 pts had reached RES (27 stage III (8 in transit only), 6 IIIB, 1 V600E, 12 LDH >ULN). At RES, 17/33 (52%) had pCR, 16 (48%) had cR (RR 88%), and 18 (46%) had mCR. The pathological response was discordant with RECIST response in 7 (21%) pts and metabolic response in 9 (27%) pts; only 11 (35%) pts with pCR had cR and mCR. No pt discontinued D+T and no pt progressed during the neoadjuvant period, D+T did not make surgery more difficult in any pt, and in 16 (48%) surgery was deemed easier. Median F/U post RES was 12.1 mo (95% CI 8.8-14.4). 12 (36%) pts had recurrent disease (median 12.9 mo), 4 while on D+T, 6 wks prior to RES, 8 at distant sites, and 1 pt had died. 26 (79%) pts developed drug fever. 18 (55%) had ≤ 1 surgical complication post RES. 11 had a wound infection requiring antibiotics, 5 had a seroma, 2 Medlated data will be presented including tumour biopsy and ctDNA biomarker data.

Conclusions: Neoadjuvant D+T has a high response rate and high pCR rate in resectable stage III melanoma. Surgical complication rates were consistent with historic conflicts of interest.

Disclosure: Funding: Legal entity responsible for the study:

Eligible pts had ECOG PS ≤ 1 with histologically confirmed resectable bulky AJCC v7 stage III(B/C) BRAF V600 mutant melanoma. CT and PET scans were performed at baseline and 12 wks just prior to RES for RECIST and metabolic complete response (cR and mCR respectively). CT monitoring was continued 12 wks thereafter to 2 yrs then 6 moly thereafter until 3 yr post-op. CD8+ T cell count at baseline and by week 1. The primary endpoint was the complete pathological response (pCR) and RECIST response rate (RR) at wk 12. Secondary endpoints were surgical morbidity, mCR, relapse free survival (RFS), OS, toxicity and translational endpoints.

Results: At data cut 18 April 2017, 35 pts had commenced D+T. 33 pts had reached RES (27 stage III (8 in transit only), 6 IIIB, 1 V600E, 12 LDH >ULN). At RES, 17/33 (52%) had pCR, 16 (48%) had cR (RR 88%), and 18 (46%) had mCR. The pathological response was discordant with RECIST response in 7 (21%) pts and metabolic response in 9 (27%) pts; only 11 (35%) pts with pCR had cR and mCR. No pt discontinued D+T and no pt progressed during the neoadjuvant period, D+T did not make surgery more difficult in any pt, and in 16 (48%) surgery was deemed easier. Median F/U post RES was 12.1 mo (95% CI 8.8-14.4). 12 (36%) pts had recurrent disease (median 12.9 mo), 4 while on D+T, 6 wks prior to RES, 8 at distant sites, and 1 pt had died. 26 (79%) pts developed drug fever. 18 (55%) had ≤ 1 surgical complication post RES. 11 had a wound infection requiring antibiotics, 5 had a seroma, 2 Medlated data will be presented including tumour biopsy and ctDNA biomarker data.

Conclusions: Neoadjuvant D+T has a high response rate and high pCR rate in resectable stage III melanoma. Surgical complication rates were consistent with historic conflicts of interest and stage of disease.

Clinical trial identification: NCT01972347

Legal entity responsible for the study: Melanoma Institute Australia

Funding: Novartis

Disclosure: A.M. Menzies: Advisory board - MSD, Novartis, Chugai, Pierre Fabre. Horizon Blue - Bristol-Myers Squibb, Roche G.V. Long: Long Advisory board - Bristol-Myers Squibb, MSD, Novartis, Amgen, Pierre Fabre. All other authors have declared no conflicts of interest.

Regional differences in overall survival (OS) in patients with advanced melanoma (MEL) who received nivolumab (NIVO) combined with ipilimumab (IPI) or NIVO alone in a phase 3 trial (CheckMate 067)


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Background: NIVO + IPI and NIVO significantly improved PFS and OS vs. IPI alone in the CheckMate 067 study. Descriptively, NIVO + IPI showed longer OS than NIVO (hazard ratio: 0.88), with 2-year OS rates of 64% and 59%, respectively. Post-hoc analyses by region were performed to evaluate potential differences between patients (pts) treated in the EU and those treated in the USA.

Methods: Baseline patient characteristics, safety and efficacy were evaluated in the two highest enrolling regions (EU, 55% and USA, 22%) using data from the CheckMate 067 study. Minimum follow-up of the pts was 28 months.

Results: EU pts were more likely to have M1c disease than USA pts (60% vs 53%), and more likely to have BRAF wild-type (WT) tumors (69% vs 59%). In a multivariate analysis, which adjusted for baseline factors, the only significant interaction between NIVO + IPI and NIVO was by region. Adjusted hazard ratios (HRs) for OS in the NIVO + IPI vs NIVO groups were 0.90 (0.66–1.23) for the EU and 0.53 (0.29–0.98) for the USA. Across all arms, 2-year OS rates were lower in the EU vs USA pts, particularly for pts with BRAF WT tumors (Table). In pts with BRAF mutant tumors, similar OS outcomes were observed between regions. Treatment exposure, safety, management of adverse events, and use of subsequent therapies did not differ substantially between the two regions. Objective response rates and progression-free survival were also similar between the two regions.

Conclusions: Differences in OS between the EU and the USA appear to be largely due to poorer survival outcomes in EU pts with BRAF WT tumors, which likely impacted OS differences between NIVO + IPI and NIVO in the overall population. Additional analyses by region, the first report of 3-year OS, as well as analyses by tumor mutation burden will be presented. Acknowledgment: J. Larkin and J.D. Wolchok contributed equally to this study.

Clinical trial identification: NCT01844505
CheckMate 067 trial.

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Background: We compared quality-adjusted survival (OS) of combined NIVO+IPI or NIVO alone vs IPI among treatment-naïve patients (pts) with advanced melanoma (MET) a quality-adjusted time without symptoms or toxicity (Q-TWiST) analysis

Methods: The Q-TWiST approach was used to partition OS into 3 health states: time without disease progression or symptoms of toxicity (TWIST), time with grade ≥ 3 treatment-related AE toxicity after randomization but before progression (TOX), and time after progression (REL). Q-TWiST was calculated by multiplying mean time spent in each state at 36 months (mos) by their utility (TWIST=1.0, TOX=0.5, REL=0.5). Q-TWiST differences were assessed at various times ranging from 3 to 36 mos. A ≥ 15% relative Q-TWiST gain (vs mean IPI OS) was considered clearly clinically important.

Results: Compared with IPI, NIVO+IPI pts had longer (difference in mean mos, 95% CI) TWIST (9.6, 7.4 to 11.7) and TOX (0.3, 0.1 to 0.4) but shorter REL time (-1.5, -2.7 to -0.3). Compared with IPI, NIVO pts had a longer TWIST (7.3, 5.0 to 9.6), shorter REL time (-3.4, -5.5 to -1.3), and shorter TOX (-0.1, -0.2 to 0.1). Q-TWiST was highest for NIVO+IPI followed by NIVO, and IPI (Table). Relative Q-TWiST gains were also favorable for NIVO+IPI (+54.0% v IPI) and NIVO (+26.4% v IPI) and increased as follow-up increased from 3 to 36 mos for all comparisons.

Conclusions: At 36 mos, NIVO and NIVO+IPI pts had a clinically important improvement in Q-TWiST vs IPI. As these benefits continue to accrue over time, future analyses with longer follow-up are planned.

Table: 1223PD

<table>
<thead>
<tr>
<th>2-yr OS rates</th>
<th>ITT Population</th>
<th>EU</th>
<th>USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>BRAF WT</td>
<td>BRAF Mutant</td>
<td>Overall</td>
</tr>
<tr>
<td>N</td>
<td>Rate</td>
<td>N</td>
<td>Rate</td>
</tr>
<tr>
<td>NIVO+IPI</td>
<td>314</td>
<td>64%</td>
<td>177</td>
</tr>
<tr>
<td>NIVO</td>
<td>316</td>
<td>59%</td>
<td>170</td>
</tr>
<tr>
<td>IPI</td>
<td>315</td>
<td>45%</td>
<td>170</td>
</tr>
<tr>
<td>HR</td>
<td>0.88</td>
<td>0.90</td>
<td>1.03</td>
</tr>
<tr>
<td>(95% CI)*</td>
<td>(0.69–1.12)</td>
<td>(0.66–1.23)</td>
<td>(0.72–1.48)</td>
</tr>
</tbody>
</table>

*NIVO+IPI vs NIVO.

Legal entity responsible for the study: Bristol-Myers Squibb

Funding: Bristol-Myers Squibb

Disclosure: J.J. Grob served as a consultant for Bristol-Myers Squibb, GSK, Novartis, Roche, Merck, Amgen, participated on speakers’ board for Bristol-Myers Squibb, GSK, Roche, traveling fund from Roche; recipient of research funding from Bristol-Myers Squibb and Roche. D. Schadendorf served as a consultant or advisor for Roche/Genentech, Novartis, Bristol-Myers Squibb, Merck Sharp & Dohme, Merck Serono, Symex, Amgen, Grunenthal Group, Immunocore; participated on a speakers’ board for Roche, Bristol-Myers Squibb, Merck Sharp & Dohme; Novartis, Amgen, Incyte, Pierre Fabre; traveling fund from Roche/Genentech, Bristol-Myers Squibb, Amgen, Merck, Merck Serono, Novartis; paid honoraria from Roche/Genentech, Novartis, Amgen, Bristol-Myers Squibb, Merck Sharp & Dohme, Symex, Immunocore, Grunenthal Group, Merck Serono, Agerus, Array BioPharma, LEO Pharma, Incyte, Pfizer, Pierre Fabre, Philogen, Regeneron; received institutional research funding from Bristol-Myers Squibb and Novartis. J. Wagstaaff: Paid honoraria from Bristol-Myers Squibb, Merck, Roche, Astellas, Pfizer, Novartis; Consultant for Bristol-Myers Squibb, Merck, Roche, Astellas, Pfizer, Novartis; participated in speakers’ board for Bristol-Myers Squibb, Novartis, Astellas; traveling fund from Bristol-Myers Squibb, Novartis, Astellas; I. Mariquez-Rodas: Paid honoraria from Novartis, Roche, MSD, Bristol-Myers Squibb; served as a consultant for Novartis, Roche, MSD, Bristol-Myers Squibb, Amgen, Bioncotech, traveling fund from MSD, Bristol-Myers Squibb, Amgen C. Lebbé: Served on an advisory board for Bristol-Myers Squibb, Roche, GSK, and Novartis; M.B. Atkins: Served as a consultant or advisor for Pfizer and Genentech. M.B. Atkins: Served as a consultant or advisor for Pfizer and Genentech. M. Botteman: Employed by and owns stock in Pharmerit International. Pharmerit International has received research funding from BMS to conduct this research. Merck International is a global health economics and outcomes research consulting firm that receives research funding and fees related to consulting and other advisory roles from numerous private organizations from the pharmaceutical, biotech, device, and medical industry. R. Shah, L. Luo: Employed by Pharmederit International. Pharmederit International has received research funding from BMS to conduct this research. K. Gupte-Singh, S. Rao: Employed by and owns stock in Bristol-Myers Squibb. D.F. McDermott: David McDermott served as a consultant or advisor for GNE, Pfizer, Novartis, GSK, C-Cam, X4 Pharma, Amgen, Lilly, Alkermes, Infinity Pharmaceuticals, Genoptix, Bristol-Myers Squibb, Nektar, Merck; received honoraria from Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

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Background: Treatment with checkpoint inhibitors can result in durable responses and deepening of responses over time with conversion of SD to PR or CR, and PR to CR. In the randomized KEYNOTE-002 study (NCT01704287), pembrolizumab 2 mg/kg or 10 mg/kg improved PFS (HR 0.57 and 0.50; p < 0.0001 for both) vs ipilimumab in pts with ipi-refractory melanoma. In this post hoc analysis, we assessed evolution of response and survival for 361 pembrolizumab-treated pts.

Methods: Pts were treated until disease progression (PD), unacceptable toxicity or investigator’s clinical decision. Response (RECIST v1.1; investigator review) was assessed at wk 12, every 6 wk until wk 48, then every 12 wk, and confirmed by subsequent scan. Survival was assessed every 12 wk during follow-up. Pembro arms were grouped according to no difference in efficacy of doses.

Results: As of 3 Feb 2017, median follow-up duration was 42.7 mo. In pembrolizumab-treated pts, median PFS was 4.2 mo (95% CI 3.3-5.6), and 36-mo PFS rate was 16%. Median OS was 14.0 mo (11.8-16.2), and 36-mo OS rate was 30%. 99 of 361 pts had CR (33%), 29 had PR (8%), and 29 were SD (8%). 9 (31%) pts with CR, 28 (40%) with PR and 63 (22%) with SD were evaluable for efficacy. 64% of CR pts, 41% of PR pts, and 36% of SD pts converted to CR or PR (cycle 1: 29%; cycle 2: 7%). Median time to response was 2.9 mo. Of 29 pts with SD, 5 converted from SD to PR, 21 from PR to PD. Median time from SD to PR was 2.7 mo (range 0.9-25.2). Median DOR was not reached in pts with CR or PR (Table). Median duration of SD was 6.9 mo (range 0.8+ to 38.8), 9 (31%) pts with CR, 28 (40%) with PR and 63 (72%) with SD had subsequent PD; in these pts, median duration of CR was 17.3 mo (5.3-36.1), 7.7 mo (2.0-31.8), and 5.8 mo (2.7-25.3). Median PFS and OS were longer in pts with CR or PR (Table).

Conclusions: Responses to pembro are durable and associated with prolonged OS in ipi-refractory melanoma. Even in these heavily pretreated pts best response can evolve over time, with late conversions from SD to PR/CR and PR to CR.

Clinical trial identification: nct.437.002 ClinicalTrials.gov NCT01704287 88) All-treated (N = 361)

Legal entity responsible for the study: Merck & Co., Inc.

Table: 1224PD

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>CR (n = 29)</th>
<th>PR (n = 70)</th>
<th>SD (n = 88)</th>
<th>All-treated (N = 361)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to response*, mo (range)</td>
<td>2.9 (2.4-24.9)</td>
<td>2.9 (1.9-27.9)</td>
<td>—</td>
<td>2.9 (1.9-27.9)</td>
</tr>
<tr>
<td>Median DOR, mo (range)</td>
<td>NR (5.5-41.6+)</td>
<td>NR (19.4+ to 43.5+)</td>
<td>6.9 (0.8+ to 38.8+)†</td>
<td>NR (19.4+ to 43.5+)</td>
</tr>
<tr>
<td>Median PFS, mo (95% CI)</td>
<td>41.0 (38.9-NR)</td>
<td>35.8 (27.9-NR)</td>
<td>7.0 (5.8-9.7)</td>
<td>4.2 (3.3-5.6)</td>
</tr>
<tr>
<td>12/24/36-mo PFS rate*</td>
<td>97%/75%/72%</td>
<td>76%/66%/49%</td>
<td>24%/6%/1%</td>
<td>29%/21%/16%</td>
</tr>
<tr>
<td>Median OS, mo (95% CI)</td>
<td>NR (NR-NR)</td>
<td>NR (NR-NR)</td>
<td>16.5 (13.8-20.5)</td>
<td>14.0 (11.8-16.2)</td>
</tr>
<tr>
<td>12/24/36-mo OS rate*</td>
<td>100%/93%/89%</td>
<td>96%/86%/71%</td>
<td>7.1%/31%/24%</td>
<td>55%/37%/30%</td>
</tr>
</tbody>
</table>

*Best overall response with confirmation.

Disclosure: A. Daud: Received research funding from and is an advisory board member of Merck & Co., Inc. R. Dummer: Received honoraria from MSD, Merck & Co., Inc.’s international counterpart. D. Schadendorf: Received research, honoraria and travel funding from Merck & Co., Inc. Serves as an advisory board member of speaker’s bureau for Merck & Co., Inc. O. Hamid: Serves on an advisory board for and has received research funding from Merck & Co., Inc., C. Robert: Received honoraria from Merck & Co., Inc. P. S. Hodi: Advisory board member for Merck & Co., Inc. A. Pavlick: Been a consultant for Merck & Co., Inc. R. Gonzalez: Received travel funding, research grants and honoraria from Merck & Co., Inc. S. J. O’Day: Served on advisory board and on speaker’s bureau for Merck & Co., Inc. Received honoraria from Merck & Co., Inc. S. J. O’Day: Received research funding for and served as an advisory board member of Merck & Co., Inc. A. K. Salama: Received research funding for and has been an advisory board member of Merck & Co., Inc. K. Margolin: Received research funding from Merck & Co., Inc. J. Yang: Employee of Merck & Co., Inc. and may own stock options in the company. B. Hornet Moreno: Employee of Merck & Co., Inc. and may own stock options in the company. N. Ibrahim: Employee of Merck & Co., Inc. and may own stock options in the company. A. Ribas: Received honoraria from Merck & Co., Inc. All other authors have declared no conflicts of interest.

Funding: Merck & Co., Inc.

Disclosures: A. Daud: Received research funding from and is an advisory board member of Merck & Co., Inc. R. Dummer: Received honoraria from MSD, Merck & Co., Inc.’s international counterpart. D. Schadendorf: Received research, honoraria and travel funding from Merck & Co., Inc. Serves as an advisory board member of speaker’s bureau for Merck & Co., Inc. O. Hamid: Serves on an advisory board for and has received research funding from Merck & Co., Inc., C. Robert: Received honoraria from Merck & Co., Inc. P. S. Hodi: Advisory board member for Merck & Co., Inc. A. Pavlick: Been a consultant for Merck & Co., Inc. R. Gonzalez: Received travel funding, research grants and honoraria from Merck & Co., Inc. S. J. O’Day: Received research funding for and served as an advisory board member of Merck & Co., Inc. A. K. Salama: Received research funding for and has been an advisory board member of Merck & Co., Inc. K. Margolin: Received research funding from Merck & Co., Inc. J. Yang: Employee of Merck & Co., Inc. and may own stock options in the company. B. Hornet Moreno: Employee of Merck & Co., Inc. and may own stock options in the company. N. Ibrahim: Employee of Merck & Co., Inc. and may own stock options in the company. A. Ribas: Received honoraria from Merck & Co., Inc. All other authors have declared no conflicts of interest.

References:

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Patients achieving CMR1 had significantly better outcome than patients achieving CMR2 in terms of PFS (HR 0.18, 95% CI 0.05-0.62) and OS (HR 0.23, 95% CI 0.06-0.85). Similar results were observed comparing CMR1 over no CMR in PFS (HR 0.19, 95% CI 0.06-0.64) and in OS (HR 0.25, 95% CI 0.07-0.87). There was no difference between the CMR2 and noCMR groups in terms of PFS or OS.

Conclusions: Attainment of CMR on an early D10-14 PET was highly predictive of long-term survival with BRAF and MEK inhibition. However, attainment of CMR at a later time point at D35-49 did not appear predictive of a survival benefit. In fact, no difference in PFS or OS could be observed in patients who achieved CMR at D35-49, compared to those patients who did not attain CMR. Correlative science analysis to investigate the mechanism of these observations are underway.

Clinical trial identification: number: NCT01721803

Legal entity responsible for the study: Genentech Roche

Funding: Genentech Roche

Disclosure: J. Frederickson: Employer of Genentech and has Roche stocks. D. Colburn, N. Choong, M. Wengenlang: Employee of Roche-Genentech. All other authors have declared no conflicts of interest.

Five-year efficacy and safety update from METRIC: Trametinib in chemotherapy in patients with BRAF V600E/K-mutant advanced or metastatic melanoma


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Background: BRAF mutations are found in 50% of patients (pts) with advanced melanoma. Previously, the METRIC trial (NCT01245062) demonstrated that the MEK inhibitor trametinib (T) increased PFS in this population of patients with a clinical benefit that could last ≥2 yrs in some pts. We report findings from the 5-year follow-up analysis.

Methods: METRIC is an open-label, randomized Phase III study of pts who received ≤1 prior regimen of chemotherapy (C). Pts were randomized (2:1) to T (2 mg/day) or intravenous C (dacarbazine [1000 mg/m²] or paclitaxel [175 mg/m²] every 3 wks). Pts were stratified according to baseline lactate dehydrogenase level and previous C for advanced disease. Pts who progressed on C were allowed to cross over to receive C. We report data from the 5-year follow-up analysis. Pts with extended follow-up after initiation of T, contributed to long-term survival for those randomized to the C-arm.

Clinical trial identification: NCT01245062

Legal entity responsible for the study: Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

Funding: Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

Disclosure: D. Schadendorf: Reports grants and personal fees from Novartis, MSD/ Merck, Amgen, GSK, Symex, Boehringer Ingelheim, Bristol-Myers Squibb, outside the submitted work K.T. Flaherty: Consulted for Novartis in relation to this abstract P. Nathan: Reports personal fees from the submitted work C. Garbe: Reports grants and personal fees from Novartis, during the conduct of the study; personal fees from Amgen, MSD, Philogen, grants and personal fees from Roche and Bristol-Myers Squibb, outside the submitted work. P. Mohr: Reports personal fees and other from Novartis, during the conduct of the study; personal fees and other from Amgen, grants, personal fees and other Bristol-Myers Squibb, MSD, Merck, Roche, outside the submitted work. J.C. Hassel: Reports other from GSK, during the conduct of the study; personal fees from Bristol-Myers Squibb, MSD, Novartis, GSK, MSD, other from MSD, Bristol-Myers Squibb, Novartis, outside the submitted work. P. Rutkowski: Reports personal fees from Novartis, Bristol-Myers Squibb, Roche, MSD, GSK, Amgen, outside the submitted work J. Dummer: Receives research funding and has a consultant or has advisory board relationship with Novartis, MSD, Bristol-Myers Squibb, Roche, GSK, Amgen, outside the submitted work J. Utikal: Reports to be on the advisory board and has received travel support from Amgen, Bristol-Myers Squibb, GSK, MSD, Novartis and Roche F. Kiecker: Reports personal fees from Amgen, personal fees from Bristol-Myers Squibb, personal fees from MSD, personal fees from Novartis, personal fees from Roche, outside the submitted work J. Larkin: Research support, Bristol-Myers Squibb, MSD, Novartis, Pfizer, Consultancy; Eisa, Bristol-Myers Squibb, MSD, GSK, Kymab, Pfizer, Novartis, Roche/Genentech, Secarna, Pierre Fabre, IUSA, Support, NIHBR IM/CR Biomedical Research Centre for Cancer A. D’Amelio Jr: Reports personal fees from Novartis Pharmaceuticals, during the conduct of the study; other from Novartis Pharmaceuticals, other from GlaxoSmithKline, outside the submitted work Y. Huang: Employee of Novartis B. Mockesy: Employee of Novartis, stock and other ownership. Novartis, GSK, Incyte, AstraZeneca C. Robert: Participated in advisory boards for Roche, GSK, Merck, Novartis, Amgen, Bristol-Myers Squibb, Novartis. All other authors have declared no conflicts of interest.

Five-year efficacy and safety update from METRIC: Trametinib in chemotherapy-naive patients with distant metastatic Merkel cell carcinoma (mMCC)

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Background: MCC is a rare, aggressive skin cancer. In a phase 2 study of patients with mMCC, progressed on or after chemotherapy (JAVELIN Merkel 200; NCT01315547), avelumab (a human anti-PD-1/L1 antibody) showed durable responses and a manageable safety profile, including an objective response rate (ORR) of 33.0%, proportion of responses with ≥1-year duration of 74% (Kaplan-Meier estimate), and estimated 1-year overall survival (OS) rate of 52%. Based on these results, avelumab was approved by the US FDA in March 2017 and is the only approved treatment for patients with mMCC. Here, we report early interim results from patients with mMCC receiving first-line avelumab.

Methods: Eligible patients with mMCC and no prior systemic treatment for metastatic disease received avelumab 10 mg/kg Q2W. Tumors were assessed every 6 weeks (RECIST v1.1) by independent review committee (IRC). Adverse events (AEs) were assessed by NCIC CTCAE v4.0.

Results: At data cutoff on Dec 30, 2016, 29 of 112 planned patients had been enrolled. Median follow-up was 3.1 months (range 0.3–8.5) and median duration of treatment was 8.1 weeks (range 2.0–37.9). Of 16 patients with ≥12 weeks of follow-up, confirmed ORR by IRC was 62.5% (95% CI 35.4–84.8) with response ongoing in all 10 patients, including in all 5 patients with ≥6 months of follow-up. Of 25 patients with ≥6 weeks
of follow-up, unconfirmed ORR by IRC was 68.0% (95% CI 46.8–85.1); responses were ongoing at last follow-up in 16 of 17 responders (94.1%; censored due to other therapy). 23 of 29 patients (79.3%) had a treatment-related AE (TRA), including 5 (17.2%) with a grade 3 or 4 TRA. There was 1 immune-mediated TRAE (grade 1 rash). 3 patients (17.2%) discontinued avelumab due to a TRAE. There were no treatment-related deaths. Updated analyses of 39 patients will be presented (n = 29 and n = 14 with ≥12 weeks and ≥6 months of follow-up, respectively; data cutoff Mar 24, 2017), including PFS and OS analyses.

Conclusions: First-line avelumab treatment resulted in early responses and a high ORR in distant mMCC, substantiating prior findings with second-line or later avelumab treatment. Most responses were ongoing, including all responders with ≥6 months of follow-up. Enrollment is ongoing.

Clinical trial identification: NCT02155647 EMR100070-003

Disclosure: R. Dummer: Received research funding from Novartis, Merck, Bristol-Myers Squibb, Roche, and GlaxoSmithKline and has served as a consultant/advisory board for Novartis, Merck, Bristol-Myers Squibb, Roche, GlaxoSmithKline, Amgen, and Takeda. M. Migden: Participated on advisory boards and received honoraria from Genentech, Inc.; Novartis Pharmaceuticals Corporation; Eli Lilly and Company; and Sun Pharmaceuticals.

1230P Modulation of Risk and Prognosis of Cutaneous Melanoma Patients by Genetic Polymorphisms on PDCD1 Gene

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Background: This study aimed to evaluate whether PD1.1 (c.4060G>A), PD1 (c.627T>C21), PD1.5 (c.804C>T) and PD1.9 (c.644C>T) single nucleotide polymorphisms (SNPs) on PDCD1 gene influence risk, clinicopathological aspects and survival of patients with cutaneous melanoma (CM).

Methods: We evaluated 250 CM patients diagnosed at the University of Campinas and 250 blood donors (controls). DNA was analyzed by real-time polymerase chain reaction (PCR) for genotyping. PDCD1 gene expression and PD1 protein expression were assessed by quantitative PCR and flow cytometry, respectively. The statistical significance of differences between groups was calculated using the Fisher’s exact or chi-square test. Bonferroni method was used in multiple comparisons. PDCD1 expression and PD1 expression on T lymphocytes were calculated, using Kruskal-Wallis and Mann-Whitney test, respectively. The prognostic impact of SNPs on recurrence-free survival (RFS) and overall survival (OS) of CM patients were examined using the Kaplan-Meier and Cox analyses.

Results: Individuals with PD1.1 CC genotype isolated and associated with PD1.5 CC (P < 0.04) and PD1.9 CT (P = 0.03) affected greater risks of developing CM, respectively. Individuals with phototype I or II and PD1 CC genotype or PD1.5 CC genotype had 5.89 and 6.71 more chances of presenting CM than others, respectively. PD1.5 TT genotype was associated with increased expression of PDCD1 gene when compared with CT or CC genotype (P < 0.03). PD1.5 CT or TT genotypes and T allele increased expression of PD1 protein in CD4+ lymphocytes (P = 0.01, P = 0.06, respectively). At 60 months of follow-up, shorter RFS was observed in patients with PD1.1 AA genotype (33.3% vs 72.5%, P = 0.02). Patients with PD1.1 AA genotype had 4.39 more chances of presenting tumor progression or relapse in univariate Cox analysis (P = 0.04) and patients with PD1.5 CC genotype had 2.38-fold increased risk of evolving to death in multivariate Cox analysis (P = 0.02).

Conclusions: The data suggest, for the first time, preliminary evidence that inherited abnormalities in regulation of T lymphocyte activities, related to PD1.1, PD1 and PD1.5 SNPs, alter CM risk and prognosis.

Legal entity responsible for the study: Faculty of Medical Sciences, University of Campinas

1231P Role of an intrinsic polymorphism in the CREB1 gene, involved in melanogenesis, with the risk and the aggressiveness of cutaneous melanoma

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Background: Recently, we observed 12,882 new single nucleotide polymorphisms (SNPs) associated with cutaneous melanoma (CM) risk in 103 patients and 103 controls, using large-scale genotyping with microarrays. CREB1 c.303 > 373G>A, involved in melanogenesis and located in regulatory sequence of mRNA processing (splicing), was selected for further analyses. An in silico analysis showed that referred SNP may alter the binding sites of splicing regulatory proteins, such as SF1 and hnRNP A1. However, the role of this SNP in the risk, aggressiveness and prognosis of CM is unknown. Verifying whether the distinct genotypes of CREB1 c.303 > 373G>A influence the CM risk and prognosis, clinicopathological aspects, and CREB1, SF1 and HNRNP A1 mRNA levels.

Methods: Genomic DNA of 262 patients and 280 controls was analyzed by RT-PCR. Patients were treated with conventional procedures. Gene expressions were determined.

Disclosures: All authors have declared no conflicts of interest.
by qPCR using total RNA of 56 controls. Chi-square, logistic regression model, Mann-Whitney and Student’s t tests analyzed the differences between groups. Progression-free survival (PFS) and overall survival (OS) times were calculated using Kaplan-Meier and Cox regression analyses.

Results: CREBI GA or AA genotypes were more frequent in CM patients than in controls (72.0% vs. 61.1%, P = 0.02). Carriers of the genotypes were under 1.61-fold increased risk of CM (95% CI: 1.07-2.41) than others. An excess of CREBI AA variant genotype was seen in patients with Breslow’s thickness higher than 1.5mm (28.2% vs. 18.3%, P = 0.04) and high Clark’s level (26.2% vs. 13.3%, P = 0.02). The median of follow-up of CM patients was 76 months; no association of referred SNP and patients’ PFS and OS was observed in this study. Individuals with CREBI GA or AA genotypes presented higher mRNA expression of CREBI (0.94 vs. 0.60 arbitrary units (UAs), P = 0.007), SFI (1.33 vs. 1.05 UAs, P = 0.05) and HNRNPA1 (0.77 vs. 0.57 UAs, P = 0.02) than those with GG wild-type genotype.

Conclusions: Our data suggest, for the first time, that CREBI c.303 + 373G>A SNP is an important hereditary factor for the risk and aggressiveness of CM, possibly due to variation of the splicing factors.

Legal entity responsible for the study: University of Campinas

Funding: Foundation for protection of research in the state of São Paulo (FAPESP)

Disclosure: All authors have declared no conflicts of interest.

1233P Investigation of AMBRA1 as a melanoma susceptibility gene

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Background: Melanoma is the most lethal form of skin cancer, which shows a rapid increase in incidence in many countries including Sweden. To date, the annual increase is over 5% and there is an urgent need to improve possibilities for prevention and early diagnosis when the prognosis is far favorable compared to disseminated disease. Melanoma is caused by an interplay of environmental and genetic factors and is one of the cancer forms showing highest heritability. Still a substantial extent of the genes underlying melanoma susceptibility is unknown.

Methods: We have executed whole-exome sequencing of melanoma-prone families to identify novel melanoma predisposing genes. Further genetic and functional studies of strong candidate genes using patient samples and melanoma cell lines has been performed. Various in vitro assays have been used to determine the role of those genes in for example autophagy and cell proliferation.

Results: One gene discovered was the autophagy/beclin-1 regulator 1 (AMBRA1), where a putative splice variant was co-segregating with the melanoma phenotype in a 4-case family. This mutation was not found among over 6000 Swedish population-based controls nor in any additional melanoma patients. AMBRA1 is essential in the regulation of autophagy and apoptosis and has been suggested to function as a tumor suppressor. By gene expression analysis we identified several transcripts of AMBRA1, with differential expression in melanoma tumors and in various melanoma cell lines. In tumor material from the splice variant carrier AMBRA1 showed low levels of expression. In melanoma cell lines, AMBRA1 was up-regulated when adding an autophagy activating reagent while down-regulated when treating the cells with Chloroquine, a drug inhibiting autophagy. AMBRA1 was also significantly up regulated when treating the cells with Crizotinib, a drug that targets the tyrosine kinase receptor c-MET and may induce autophagy, whereas no effect was seen when using the BRAF-inhibitor Vemurafenib. Thus, AMBRA1 may be involved in the Crizotinib-induced autophagy pathway.

Conclusions: Preliminary data suggest AMBRA1 as a candidate melanoma susceptibility gene with a role during autophagy in melanoma cells. Further studies are needed to elucidate the specific role of this gene in melanoma development.

Legal entity responsible for the study: Karolinska Institutet

Funding: The Swedish Cancer Society, The Swedish Research Council, Regneri foundation

Disclosure: All authors have declared no conflicts of interest.

1234P Hybrid-capture based genomic profiling identifies BRAF V600 and non-V600 alterations in melanoma samples negative by prior testing

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Background: BRAF and MEK inhibitors are approved for V600-mutated melanoma, and response rates of up to 70% are seen for patients with V600 mutations. Responses to targeted therapies have also been observed for a variety of non-V600 BRAF alterations. Thus, sensitive, accurate, and broad detection of BRAF alterations is critical to maximizing patients with available targeted therapy.

Methods: Pathology reports were reviewed for 385 consecutive melanoma cases (Mar 2016 - Mar 2017) with BRAF mutations or rearrangements identified using a hybrid-capture based next generation sequencing (NGS) assay during the course of clinical care.

Results: Records of prior BRAF molecular testing were available for 79 (21%) cases, utilizing PCR (n = 30), Sanger sequencing (n = 13), IHC (n = 10), non-hybrid capture based NGS (n = 9), or other or unspecified methodology (n = 17). Of cases with BRAF V600 mutations 11/57 (19%) were negative by prior BRAF testing, including 2/11 (18%) with confirmation that the same biopsy was tested. In cases with BRAF V600 mutations, there was no significant difference in mutant allele frequencies (median 0.9% vs. 0.2%, p = 0.25) or percentage of tumor nuclei (median 36% for both, p = 0.97) between samples with prior negative and prior positive results. Prior negative results were also identified in 16/20 (80%) cases with non-V600 mutations, two of which harbored multiple BRAF alterations [R061E (4), L593A/G (4), G467L (2), L585F (2), G464V, G466V, G469V, E586K, N581L, L597Q, A589_T599insT]. Two of 2 (100%) cases with activating BRAF fusions also had prior negative BRAF results.

Clinical outcomes for a subset of patients will be presented.

Conclusions: Despite approved companion diagnostics, significant variability exists in methods for BRAF testing in the clinical setting. Hybrid-capture based NGS identifies diverse activating mutations and fusions, including BRAF V600E, in a significant fraction of cases for which prior BRAF testing returned negative results. Given the proven clinical benefit in patients with BRAF alterations treated with matched targeted therapies, hybrid-capture based NGS should be considered for patients with metastatic melanoma, particularly if other testing is negative.

Legal entity responsible for the study: Foundation Medicine, Inc.

Funding: Foundation Medicine, Inc.

Disclosure: A. Wang, J.S. Ross, P.J. Stephens, S.M. Ali, A.B. Schrock, V.A. Miller. Employee with stock ownership in Foundation Medicine, Inc. All other authors have declared no conflicts of interest.

References:

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doi:10.1093/annonc/mdx377 | 437
**Background:** The complex interface between T lymphocytes and cancer (‘the immunological synapse’) comprises both co-stimulatory and co-inhibitory proteins that modulate lymphocytes towards activation or anergy. ‘Checkpoint inhibitors’ have impressive activity in melanoma, but not all patients respond and drug resistance often develops. miRNAs are master regulators of gene expression. Our aim is to study the regulation of the immunological synapse by miRNAs in melanoma.

**Methods:** Bioinformatical analyses of miRNAs and mRNA expression in 451 samples from the melanoma TCGA database was performed. Spearman’s rho correlation coefficients were calculated and survival analysis was performed using the Kaplan-Meier method. Direct mRNA targets of miRNAs were found using luciferase reporter assays, and miRNA/mRNA expression was assessed by qRT-PCR following either ectopic expression or depletion of specific miRNAs.

**Results:** Of 15 checkpoint miRNAs and 8 mRNA examined, nine checkpoint miRNAs showed a highly statistically significant positive correlation to each other and, to a lesser extent, to miRNA target results were found to control Gvi in vitro. Mi-16 may potentially target the 3’UTR of 5 of these miRNAs. CD80 (B7.1) was found to be a direct target of mic in vitro. Overexpression of mi-16 in melanoma cell lines led to downregulation of CD80, CD274 (PD-L1) and CD40, while downregulation of mi-16 increased the expression of the co-stimulatory molecules. Survival data from 156 stage III melanoma patients shows that high levels of mi-16 and low levels of any of six checkpoint miRNAs (among them CD80) is significantly associated with poor prognosis.

**Conclusions:** Our results suggest that mi-16 and many checkpoint miRNAs are generally under a strict joint transcriptional regulation. The ability of mi-16 to decrease CD80 expression suggests that it serves as a key regulator of the immunological sample. We hypothesize that in vivo, an aberrantly high expression of mi-16 decreases the expression of co-stimulatory checkpoint CD80 and other co-inhibitory miRNAs, leading to immune evasion and compromised outcome. Further elucidation of both the transcriptional and post-transcriptional regulation of the immunological synapse may help point to novel targets and means for immune modulation.

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**Disclosure:** All authors have declared no conflicts of interest.

**Legal entity responsible for the study:** Reyna Leibowitz-Amit

**Funding:** Israeli Scientific Foundation (ISF)

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**Post-transcriptional regulation of immune checkpoint genes by mir-16 in melanoma**

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**Background:** The BRCA2 tumor-suppressor gene has been linked to an increased risk of both breast and ovarian cancer. Genomic medicine, MD Anderson Cancer Center, Houston, TX, USA

**Methods:** A cohort of confirmed BRCA2 carriers was analyzed for incidence of cutaneous melanoma and nonmelanoma skin cancers diagnoses in a consecutive prospective cohort study. Checkpoint inhibitors have impressive activity in melanoma, but not all patients respond and drug resistance often develops. miRNAs are master regulators of gene expression. Our aim is to study the regulation of the immunological synapse by miRNAs in melanoma.

**Results:** Of 15 checkpoint miRNAs and 8 mRNA examined, nine checkpoint miRNAs showed a highly statistically significant positive correlation to each other and, to a lesser extent, to miRNA target results were found to control Gvi in vitro. Mi-16 may potentially target the 3’UTR of 5 of these miRNAs. CD80 (B7.1) was found to be a direct target of mi-16 in vitro. Overexpression of mi-16 in melanoma cell lines led to downregulation of CD80, CD274 (PD-L1) and CD40, while downregulation of mi-16 increased the expression of the co-stimulatory molecules. Survival data from 156 stage III melanoma patients shows that high levels of mi-16 and low levels of any of six checkpoint miRNAs (among them CD80) is significantly associated with poor prognosis.

**Conclusions:** Our results suggest that mi-16 and many checkpoint miRNAs are generally under a strict joint transcriptional regulation. The ability of mi-16 to decrease CD80 expression suggests that it serves as a key regulator of the immunological sample. We hypothesize that in vivo, an aberrantly high expression of mi-16 decreases the expression of co-stimulatory checkpoint CD80 and other co-inhibitory miRNAs, leading to immune evasion and compromised outcome. Further elucidation of both the transcriptional and post-transcriptional regulation of the immunological synapse may help point to novel targets and means for immune modulation.

**Legal entity responsible for the study:** Reyna Leibowitz-Amit

**Funding:** Israeli Scientific Foundation (ISF)

**Disclosure:** All authors have declared no conflicts of interest.

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**1237P Resected malignant melanoma at high risk of recurrence in SEER-Medicare**

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**Background:** While surgery remains a mainstay in the management of high-risk resectable malignant melanoma (MM), there is a high chance of recurrence. Utilization of approved adjuvant therapies (e.g. interferon α and ipilimumab) are limited by the common occurrence of debilitating side effects. The objective of our study was to describe characteristics of patients (pts) with resected MM at high risk of recurrence in the older US population.

**Methods:** A retrospective cohort study was undertaken using the Surveillance, Epidemiology, and End Results (SEER)-Medicare population-based linked database. The study population included pts with Stage I BCC surgically resected MM diagnosed between 2004 and 2011. Demographic and clinical characteristics, adjuvant therapies, including radiation (XRT) and/or systemic therapy (eg, interferon α, interleukin-2, pegylated interferon), and overall survival (OS) were evaluated.

**Results:** We identified 1016 pts; the mean age was 75.2 years (interquartile range [IQR], 72–82) and 66.2% were males. The majority of pts had Stage I BCC disease at diagnosis (Cohort 1; n = 877 [86.3%]); the remainder had stage IIIC disease (Cohort 2; n = 139 [13.7%]). Adjuvant therapy was utilized in 27.3% (n = 294) of pts in Cohorts 1 and 2, respectively, and consisted of XRT in 74% and 78% of pts, systemic therapy in 16% and 10% of pts (with interferon α representing 98.6% of systemic therapies), and a combination of XRT and systemic therapy in 10% and 12% of pts. OS differed between cohorts, with a median of 32.3 months (IQR, 17.9–53.3) for Cohort 1 and 19.8 months (IQR, 11.5–36.2) for Cohort 2. Landmark OS at 5 years was 20.8% for Cohort 1 and 12.2% for Cohort 2.

**Conclusions:** Among pts with resected MM at high risk of recurrence in the older US population, utilization of adjuvant therapy and OS varied based on disease stage at diagnosis. Pts with Stage IIIC disease were exposed to more medical interventions, however, use of highly toxic systemic therapy available during the study period was limited in both cohorts. As more therapies for the adjuvant setting are being developed, the evaluation of clinical and demographic characteristics may help tailor treatment regimens.

**Legal entity responsible for the study:** F. Hoffmann-La Roche Ltd

**Funding:** F. Hoffmann-La Roche Ltd

**Disclosure:** N. Sadetsky, A. Hernandez, D. Colburn: Employee, Genentech, Inc. G. Goodman: Employee, Genentech, Inc.; owns stock in Roche. All other authors have declared no conflicts of interest.

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**1238P Independent prognostic impact of lympho-vascular invasion in cutaneous melanoma patients with sentinel lymph node biopsy**


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**Background:** Incidence of cutaneous melanoma (CM) is increasing worldwide. The primary treatment of CM is surgery. Prognosis is determined by characteristics of the lesion such as depth of invasion, ulceration and sentinel lymph node (SLN) status. The aim of this study was to analyze the prognostic impact of lympho-vascular invasion (LVI) in CM patients’ (pts) undergoing SLN biopsy since LVI has not been established as a clear prognostic factor in the current AJCC 8th ed. cancer staging system.

**Methods:** Retrospective, descriptive and observational analytical study. We used the institutional database of pts with diagnosis of CM, submitted to SLN biopsy between November 1994 and August 2016. The association between pathological characteristics and SLN were analyzed using Chi2 and logistic regression model. Kaplan Meier and Log rank were used for disease free survival (DFS) analysis.

**Results:** 385 pts with a diagnosis of CM were analyzed. Median follow-up 45.2 months (IQR: 15.66–91.77). Median age: 52 years (IQR 42–65). SLN+: 47/384 (12.2%). Evaluated prognostic factors: Breslow (Br) 1.5 mm mid IQR 1.2–6.7, ulceration + 94/385 (24.4%), LVI+ 32/144 (22.2%). Relapse 86/367 (23.4%). In the univariate analysis we found association between ulcer and the following factors: 1. V1: n = 90/2; 29.7, p = 0.0125, SLN+ (OR: 3.97, p < 0.01), Br ≥ 1mm (OR: 4.13, p = 0.01) and ulceration + (OR: 2.08, p < 0.01). There was no association with age and sex. In the multivariate analysis LVI+ (OR: 2.47, p = 0.049) and SLN+ (OR: 3.91, p = 0.048)
were associated with relapse, whereas neither Br ≥ 1 mm, sex nor ulceration were associated with relapses. 5-year DFS was higher in SLN - (79.3% vs 56.1%, p < 0.01), LVI - (80.2% vs 57.9%, p<0.019), Br < 1 mm (89.5% vs 71%, p < 0.01) and ulceration - (89.3% vs 59.7%, p < 0.01).

Conclusions: In our retrospective series, after a long period of follow-up, the presence of LVI as an independent factor was associated with relapse and DFS. Within CM pts the best candidate for adjuvant therapy is yet to be defined. LVI ≥ as a prognostic factor should be validated in prospective trials in this scenario.

Legal entity responsible for the study: Institute Alexander Fleming
Funding: Institute Alexander Fleming
Disclosure: All authors have declared no conflicts of interest.

1239P Validating prognostic models in metastatic uveal melanoma (MUM), an international rare cancers initiative

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Background: We validated 2 models (the 7thAmerican joint committee on cancer (AJCC) and the Helsinki university central hospital (HUCH) staging) and 1 nomogram; the Padova-Mayo (PMN), for progression free (PFS) and overall survival (OS) using patient (pt) level data from the PUUMA meta-analysis.

Methods: 29 prospective trials (1988-2015) pt data was analysed. Models were validated with cox regression analysis for survival in months (m). Concordance index (CCI) was used to test predictive value.

Results: Comparable data was available for 463 pt; see table for variables used in each system. Models were prognostic differentiating into M1a, M1b and M1c groups. Median DFS for AJCC was 4m for M1a, 3 for M1b and 2 for M1c. Median DFS for HUCH was 5.4m for M1a, 2.3 for M1b and 1 for M1c. CCI for DFS using AJCC was 0.69 (SE 0.02, 95%CI 0.65-0.73), for HUCH it was 0.79 (SE 0.02, 95%CI 0.74-0.83). Median OS for AJCC was 15m for M1a, 9 for M1b and 5 for M1c. Median OS for HUCH was 13m for M1a, 6 for M1b and 2 for M1c. CCI for OS for AJCC was 0.69 (SE 0.02, 95%CI 0.65-0.73). For HUCH it was 0.79 (SE 0.02, 95%CI 0.74-0.83). Using ECOG and LDH (available variables used in PMN) median DFS was 4m (95% CI 4-5) for normal LDH and ECOG 0 and 2.6 (2-3) for elevated LDH and ECOG 0. Corresponding median OS was 17m (95%CI 15-18), 12.7 (95%CI 10-19), 7.4 (95%CI 6.3-8.9) and 5.3 (95%CI 3.8-6.1). CCI were DFS 0.72 (SE 0.02, 95% CI 0.69-0.75), OS 0.73 (SE 0.02, 95%CI 0.70-0.76).

Conclusions: Prognostic models in MUM remain imprecise in an externally validated dataset. Further validation is needed to find clinical utility.

Legal entity responsible for the study: Princess Margaret Cancer Centre
Funding: None
Disclosure: L. Khoja: Employed by AstraZeneca plc. All other authors have declared no conflicts of interest.

1240P Impact of an active surveillance programme on outcome of patients (pts) with uveal melanoma (UM) after primary curative therapy (PTx): results of a single-institution experience

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Background: About 30% of pts with UM develop metastatic disease (MUM) despite PTx. Liver is by far the commonest site of metastases. MUM has poor prognosis and no systemic treatment (STx) has been proven to improve overall survival (OS). However, the role of active surveillance for metastatic disease is still controversial.

Methods: We performed an outcome analysis of all UM pts prospectively registered onto our active surveillance programme after PTx. All pts had systemic staging at initial diagnosis of UM and then 6-monthly liver imaging (CT triple-phase or ultrasound) and clinical review for the first 5 years and 12-monthly afterwards. Progression-free survival (PFS) was calculated from time of first systemic relapse to first disease progression, OS from time of first systemic relapse to death or latest FU.

Results: Out of 166 pts registered between April 2009 and April 2017, 36 (22%) developed MUM: 14 pts relapsed <2 yrs, 17 between 2 and 5 yrs, 5 >5 yrs from PTx. MUM pts characteristics: males 19 (53%), median age 58 (range 34-85); median tumour thickness at diagnosis 9mm (2-22); sites of metastases: liver only 13 (36%), liver + other sites 21 (58%), extra-hepatic only 2 (6%). Relapses were asymptomatic and detected on surveillance imaging in 29 (80%) pts. Nine pts (7 detected from surveillance) underwent primary hepatic metastasectomy (HME), 27 (73%) pts were non-resectable (NR) and underwent STx (n = 18), locoregional Tx (n = 4), best supportive care (n = 5). Overall, 29/56 MUM pts received immunotherapy with either ipilimumab or nivolumab/pembrolizumab. At a median FU of 36.5 mos (1-103), 27 pts have died and the median OS is 16.6 mos (95%CI: 7.8-25.3). Both PFS and OS were statistically significantly longer for HM pts compared to NR pts (PFS: 10.8 vs 4.4mos, p = 0.013; OS: 24.9 vs 13.4mos, p = 0.04). Eight out of 9 pts developed further disease relapse after HM.

Conclusions: Our data indicate that active surveillance after PTx of UM can allow detection of asymptomatic potentially resectable liver metastases, especially in pts with a short-term disease-free interval.

Table: 1239P

<table>
<thead>
<tr>
<th>Variable</th>
<th>(n = 463)</th>
<th>AJCC</th>
<th>HUCH</th>
<th>PMN</th>
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<td></td>
<td>(n, %, median, range)</td>
<td>(7thAJCC)</td>
<td>(HUCH)</td>
<td>(PMN)</td>
</tr>
<tr>
<td>ECOG</td>
<td></td>
<td>&lt; 3 cm</td>
<td>3-8 cm</td>
<td>&gt; 8 cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.9 (0-2.9)</td>
<td>4.4 (3-8)</td>
<td>10.8 (8.1-22.5)</td>
</tr>
<tr>
<td>Diameter in cm of largest metastasis</td>
<td></td>
<td>&lt; 3 cm</td>
<td>3-8 cm</td>
<td>&gt; 8 cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.8 (0-22.5)</td>
<td>344 (39-8198)</td>
<td></td>
</tr>
<tr>
<td>Diameter of largest liver lesion</td>
<td></td>
<td>&lt; 20-50 &gt; 50 Missing</td>
<td>89 (24-1178)</td>
<td></td>
</tr>
<tr>
<td>% liver involvement</td>
<td></td>
<td>LDH</td>
<td>ALP</td>
<td>Disease free interval</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OS (% , 95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>M1a</td>
</tr>
<tr>
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<td></td>
<td>12</td>
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<td>24</td>
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<td>M1b</td>
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<td>12</td>
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<td>24</td>
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<td></td>
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<td></td>
<td></td>
<td>M1c</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>24</td>
</tr>
</tbody>
</table>
high risk U (i.e. tumour thickness >5mm). Although durable remission after HM is rare PFS and OS may be significantly prolonged. Legal entity responsible for the study: St Vincent’s Healthcare Group Funding: None Disclosure: All authors have declared no conflicts of interest.

1241P Impact of duration of response (DOR) on overall survival (OS) in patients with metastatic melanoma treated with dacarbazine (DTIC), ipilimumab (IPI), nivolumab (NIVO), pembrolizumab (Pembro), and lenvatinib (LEN). A pooled analysis


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Background: Evaluation of treatment efficacy in oncology using OS is confounded by survival benefit from post-progression treatment. We pooled data from the BRIM-2, -3, -7, and coBRIM studies (BRAF inhibitor–naïve patients with BRAFV600-mutated metastatic melanoma) to evaluate whether DOR could be a surrogate for OS.

Methods: Time-dependent Cox proportional hazard regression was used to model the association of DOR with risk of death (interval from first RECIST response to progressive disease [PD] or death) with OS. The risk of death for DORs of 1–10 months (in 1-month increments) was evaluated. Patients with best response of stable disease or PD (nonresponders [NR]) were assigned a DOR of zero. Models were adjusted for time-fixed baseline covariates (ECOG status, demographics, disease covariates, and first-line treatment), and time-dependent covariates (DOR and post-progression treatment [immunotherapy, targeted therapy, or other]).

Results: This analysis included 1365 patients (DTIC = 338, V = 717, C = V = 310). Objective response was 47.5% for the overall population and 11.5%, 53.6%, and 72.9% for the DTIC, V, and C cohorts, respectively. Median DOR was 9.3 months in the overall population and 6.4, 7.6, and 14.6 months in the DTIC, V, and C cohorts, respectively. Cox proportional hazards adjusted for time-dependent covariates showed a significant and progressive reduction in the risk of death with increasing DOR vs NR. The absolute risk of death decreased by a mean of 6.3–7.7% per month increase in DOR for the overall population and 6.4, 7.6, and 14.6 months in the DTIC, V, and C cohorts, respectively. Cox proportional hazards adjusted for time-dependent covariates showed a significant and progressive reduction in the risk of death with increasing DOR vs NR. Time-dependent Cox proportional hazards regression was used to model the overall population and across treatment cohorts (Table). Sensitivity analyses in responders only showed similar results.

Conclusions: These exploratory analyses suggest that DOR is independently associated with OS outcomes regardless of treatment and merits further exploration as a surrogate endpoint to assess long-term treatment benefit.

Legal entity responsible for the study: F. Hoffmann-La Roche Ltd.

Funding: F. Hoffmann-LaRoche Ltd.

Disclosure: K. Lewis: Grants from Roche/Genentech, Amgen, EMD Serono, and Incyte, and personal fees from Roche/Genentech, Incyte, and SunPharma. J. Larkin: Institutional research support from MSD, Bristol-Myers Squibb, Pfizer, and Novartis and nonremunerated consultant for GSK, Novartis, MSD, Bristol-Myers Squibb, Pfizer, and Roche/Genentech. A. Ribas: Owns stock in Kite Pharma and has received honoraria from Roche, Amgen, Pfizer, and Merck. All monies paid to Dr. Ribas are deposited into the Division Account at the David Geffen School of Medicine and do not constitute personal income. K.T. Flaherty: Consultant for Roche. G.A. McArthur: Research grant support from Pfizer, Celgene, Ventana; consultant for Provectus; uncompensated consultancy for Pfizer, Millennium, GSK, Roche/Genentech, Novartis, Bristol-Myers Squibb, and Amgen. P.A. Ascierto: Consulting or advisory role for Amgen, Array, Bristol-Myers Squibb, Genentech/Roche, Merck Serono, Merck Sharp & Dohme, Novartis, and Pierre-Fabre; and research funding from Bristol-Myers Squibb, Genentech/Roche, and Array. B. Döré: Personal fees from Roche, Bristol-Myers Squibb, Novartis, GlaxoSmithKline, and Amgen. E. McCormick: Employee, Genentech, Inc. Q. Zhu, Y. Man: Employment, Genentech, Inc. A. Hauschild: Personal fees from Roche, Amgen, Bristol-Myers Squibb, Celgene, Eisai, GlaxoSmithKline, Merck, Merck Serono, Merck Sharp & Dohme/Merck, Novartis, Oncoceutics, and MELA Sciences.

Table: 1241P Hazard of death by duration in response (excluding time-dependent PD variables)

<table>
<thead>
<tr>
<th>Patient cohort</th>
<th>DOR of 1 month HR (95% CI)</th>
<th>DOR of 10 months HR (95% CI)</th>
<th>Mean per month HR decrease</th>
<th>Range of HR decrease</th>
<th>P-valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>0.85 (0.82–0.87)</td>
<td>0.19 (0.14–0.25)</td>
<td>0.073</td>
<td>0.034–0.130</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>V</td>
<td>0.80 (0.77–0.84)</td>
<td>0.11 (0.07–0.18)</td>
<td>0.077</td>
<td>0.028–0.157</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>C+V</td>
<td>0.89 (0.86–0.93)</td>
<td>0.33 (0.23–0.46)</td>
<td>0.063</td>
<td>0.039–0.095</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DTIC</td>
<td>0.81 (0.71–0.92)</td>
<td>0.12 (0.03–0.45)</td>
<td>0.076</td>
<td>0.029–0.154</td>
<td>0.0016</td>
</tr>
<tr>
<td>All respondersa</td>
<td>0.88 (0.85–0.90)</td>
<td>0.27 (0.21–0.35)</td>
<td>0.068</td>
<td>0.038–0.108</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>V</td>
<td>0.84 (0.80–0.88)</td>
<td>0.17 (0.11–0.27)</td>
<td>0.074</td>
<td>0.033–0.135</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>C+V</td>
<td>0.91 (0.88–0.94)</td>
<td>0.37 (0.27–0.51)</td>
<td>0.059</td>
<td>0.035–0.086</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DTIC</td>
<td>0.87 (0.78–0.97)</td>
<td>0.26 (0.09–0.77)</td>
<td>0.069</td>
<td>0.037–0.111</td>
<td>0.0148</td>
</tr>
</tbody>
</table>

HR, hazard ratio.
aAssociation of DOR with risk of death.

Patients with complete or partial response.

1242P Neutrophil to Lymphocyte Ratio (NLR) as an independent prognostic measure in patients receiving targeted therapy or immunotherapy for stage IV melanoma

E. Backley1, L. Lim1, M. Moore1, M. Voskobobyn1, C. McLear1, A. Haydon1

1Medical Oncology, Alfred Health, Melbourne, Australia; 2Department of Pathology, Alfred Health, Melbourne, Australia

Background: Treatment of metastatic melanoma has rapidly evolved with the introduction of targeted and immunotherapies in recent years. An elevated NLR (neutrophil-lymphocyte ratio) has been shown to be an independent marker of poor prognosis in malignancies including melanoma. Here we present an updated survival analysis demonstrating the utility of NLR as a marker of prognosis in patients with metastatic melanoma receiving targeted and immunotherapy.

Methods: We identified patients with stage 4 melanoma who received systemic therapy with targeted therapy (BRAF +/- MEK inhibitor) or immunotherapy (Anti-CTLA-4 or Anti-PD-1) at our institution. Patients not receiving any systemic therapy were excluded. We retrospectively reviewed all medical records on patients with baseline demographics, prognostic factors (stage, LDH, CNS and Liver metastases), treatments received, pre-treatment NLR and outcomes. Overall survival (OS) and Progression-free survival (PFS) were measured from date of first dose received.

Results: 174 patients were treated between August 2010 to November 2016, 74 received targeting therapy and 100 receiving immunotherapy. Median follow up was 10 months. At time of interim analysis median OS for patients with NLR < 5 was 11.7 months compared to 4.8 months in NLR > 5 (HR 0.45, 95% CI 0.31–0.67, p = 0.00007), this was seen in patients treated with both targeted therapies (HR 0.48, p = 0.012) and immunotherapies (HR 0.40, p = 0.0009). Median PFS was also longer in patients with NLR < 5 vs. 4.8 vs. 3.6 months (HR 0.65, p = 0.02). Multivariate analysis including age, sex, M stage, baseline LDH and CNS/Liver metastases, demonstrated NLR was the strongest predictor of OS (HR 0.39 95% CI. 0.25–0.66, p = 0.00002).

Conclusions: NLR > 5 is a strong independent predictor of poor outcome in patients with metastatic melanoma regardless of targeted or immunotherapy. We hypothesis that at final data lock in July 2017 this association will remain strong given it was a clear predictor of outcome at the time of interim analysis. NLR may assist selection of initial therapy, for example, a favourable ratio may indicate suitability for single agent rather than doublet immunotherapy with its greater toxicity profile.

Legal entity responsible for the study: Alfred Health

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Results: From 380 advanced melanoma patients, 161 BRAF mutants patients received 1st line BRAFi only (101) or BRAFi+MEKi (60). Patients relapsed from primary at a median DMFI 12 months (range 0-185) and were included in the 3 prognostic groups (Group A 27, Group B 72, Group C 56). To study DMFI significance, we defined 2 patients groups according to DMFI: DMFI <24 months Group 1, DMFI >24 months Group 2. Median PRPS was 5 months for Group 1 and 8 months for Group 2 with statistically significant difference (HR = 1.45, 95%CI 1.21-2.09, p = 0.046). In multivariate analysis, DMFI also emerged as independent prognostic factor (HR 1.44, 95% CI 0.99-2.10, p = 0.059). Prognostic Group (C vs A), number of metastatic sites (≥3 vs <3), LDH (≥2ULN vs normal) were confirmed as independent prognostic factors for PRPS and PRS. ROC analysis on prognosis showed best DMFI cut-off at 26 months (95% CI 1.96 [1.10-2.33), p = 0.014 [46.2%, spec 69.6%]. No difference in median PRS between the 2 groups (14 vs 16 months, p = 0.517), possibly reflecting effect of therapies after BRAFi.

Conclusions: Patients with BRAF mutant advanced melanoma and DMFI <2 years has significantly worse post relapse PFS after 1st line targeted therapy. Our results indicate DMFI as an independent prognostic factor for BRAFi patients.

Legal entity responsible for the study: A Oncology Dept, Metropolitan Hospital

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1243P The prognostic significance of distant metastasis free interval (DMFI) in BRAF mutant advanced melanoma patients treated with first line targeted therapy

D. Boháčková, H. Linardou, P. Diamantopoulou, T. Tengeranis, A. Laskarakis, K-M. Gutiérrez, G. Gagel, M. Schadendorf, I. Krajsov Faculty, Prague, Czech Republic, 1Department of Dermatology and Allergy, Skin Oncology Dept, Metropolitan Hospital, Athens, Greece, 21st Dept of Medicine, Laikon Hospital, Medical School, National and Kapodestrian University of Athens, Athens, Greece, 3Dept of Hygiene, Epidemiology and Medical Statistics, Medical School, National and Kapodestrian University of Athens, Athens, Greece

Background: Prognostic models are investigated for advanced melanoma patients treated with targeted therapy. This study aims to identify the relationship between DMFI and outcome of 1st line targeted therapy in BRAF mutant (BRAFmut) patients.

Methods: BRAFmut patients identified from 2 referral centres were assigned to 3 prognostic groups: A (PS 0, Metastatic sites ≤3, LDH normal, CNS not involved), B (PS 1, Metastatic sites ≤3, LDH >1-2ULN, CNS not involved), C (PS 2, Metastatic sites >3, LDH >2ULN, CNS involved or not). Factors analysed: Distant Metastasis Free Interval (DMFI from primary melanoma to 1st distant metastasis), Post Relapse Progression Free Survival (PRPS post relapse to BRAFi), Post Relapse Survival (PRS), number of metastatic sites, LDH, CNS involvement, PS. Univariate and multivariate Cox regression analysis was used adjusted with the 3 prognostic groups. Statistical analysis with Stata/SE V13.0.

Results: From 380 advanced melanoma patients, 161 BRAFi patients received 1st line BRAFi only (101) or BRAFi+MEKi (60). Patients relapsed from primary at a median DMFI 12 months (range 0-185) and were included in the 3 prognostic groups (Group A 27, Group B 72, Group C 56). To study DMFI significance, we defined 2 patient groups according to DMFI: DMFI ≤24 months Group 1, DMFI >24 months Group 2. Median PRPS was 5 months for Group 1 and 8 months for Group 2 with statistically significant difference (HR = 1.45, 95%CI 1.21-2.09, p = 0.046). In multivariate analysis, DMFI also emerged as independent prognostic factor (HR 1.44, 95% CI 0.99-2.10, p = 0.059). Prognostic Group (C vs A), number of metastatic sites (≥3 vs <3), LDH (≥2ULN vs normal) were confirmed as independent prognostic factors for PRPS and PRS. ROC analysis on prognosis showed best DMFI cut-off at 26 months (95% CI 1.96 [1.10-2.33), p = 0.014 [46.2%, spec 69.6%]. No difference in median PRS between the 2 groups (14 vs 16 months, p = 0.517), possibly reflecting effect of therapies after BRAFi.

Conclusions: Patients with BRAF mutant advanced melanoma and DMFI <2 years have significantly worse post relapse PFS after 1st line targeted therapy. Our results indicate DMFI as an independent prognostic factor for BRAFi patients.

Legal entity responsible for the study: A Oncology Dept, Metropolitan Hospital

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1244P Hospitalization Rates in COLUMBUS Part 1: A Phase 3 Trial of Encorafenib (ENCO) Plus Binimetinib (BINI) Versus Vemurafenib (VEM) or ENCO in BRAF-Mutant Melanoma


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Background: Part 1 of the COLUMBUS study demonstrated that the BRAF inhibitor ENCO 450 mg once daily (QD) + the MEK inhibitor BINI 45 mg twice daily (BID;
Background: In COLUMBUS Part 1, the BRAF inhibitor ENCO 450 mg once daily (QD) + the mitogen-activated protein kinase kinase (MEK) inhibitor INK1B 45 mg twice daily (BID; COMBO450) improved progression-free survival vs VEM 960 mg BID alone and ENCO 300 mg QD (ENCO300) alone in patients (pts) with advanced BRAF V600E-mutant melanoma. Tolerability of COMBO450 was favorable compared with VEM or ENCO300. Here we compare patient-reported health-related QoL during the treatment arms.

Methods: Pts were randomized 1:1:1 to receive COMBO450, VEM, or ENCO300. Patient-reported health-related QoL was assessed by validated instruments, the Functional Assessment of Cancer Therapy–Melanoma (FACT-M) questionnaire and the European Organization for Research and Treatment of Cancer’s Questionnaire of Life-Questionnaire-Core 30 (EORTC QLQ-C30). Higher scores represent better QoL on both instruments. A mixed-effect model for repeated measures was used to compare the change from baseline (BL) in the domain scores over time.

Results: Among 577 pts, 192 were randomized to COMBO450, 191 were randomized to VEM, and 194 were randomized to ENCO300. Compliance of pts completing the FACT-M and EORTC QLQ-C30 questionnaires was equivalent; approximately 80%–90% of pts still at risk completed the assessment from BL through cycle 25. Mean BL FACT-M M scores were similar across arms (52.39, 52.01, and 52.84 in the COMBO450, VEM, and ENCO300 arms, respectively). FACT-M subscale change over time indicated that COMBO450 was associated with an estimated 2.98 point higher post-BL score vs VEM (95% CI 1.54–4.43) and a 4.01 pt higher post-BL score vs ENCO300 (95% CI 2.72–5.34). Mean EORTC QLQ-C30 scores at BL were 66.72, 64.74, and 66.10 with COMBO450, VEM, and ENCO300, respectively. Evaluation of change over time found that COMBO450 was associated with an estimated 3.25 pt higher post-BL score vs VEM (95% CI 2.12–4.39) and an 8.32 higher post-BL score vs ENCO300 (95% CI 4.54–12.11).

Conclusions: Patient-reported health-related QoL was rated consistently and significantly better with COMBO450 vs VEM or ENCO300 monotherapy.

Clinical trial identification: Trial protocol number, CMK61B2901 (release date, July 13, 2015)

Legal entity responsible for the study: Array BioPharma Inc

Funding: Array BioPharma Inc and Novartis Pharmaceuticals Corporation

Disclosure: H. Gogas: Consultant for Roche, Bristol-Myers Squibb, MSD, Novartis, and AstraZeneca. H. Gogas: Has received travel expenses from Kieffer Pharma, Roche, Bristol-Myers Squibb, MSD, and AstraZeneca. H. Gogas: Has received speaker fees from Array BioPharma, Roche, and Bristol-Myers Squibb. H. Gogas: Has received research funding from Roche, Bristol-Myers Squibb, and MSD. P. A. Ascierto: Consulting fees from Bristol-Myers Squibb, Roche, Genentech, MSD, and Novartis. E.락. Ingelheim; research funding from Roche, Novartis, Pfizer, Johnson & Johnson; travel expenses from Bristol-Myers Squibb, Roche, V. Chiarion Sileni: Honoraria received from Novartis, GSK, Bristol-Myers Squibb, MSD, and Roche; speakers bureau for Novartis, GSK, Roche, and Bristol-Myers Squibb; advisory board member for Amgen, Novartis, MSD, Bristol-Myers Squibb, and Roche. J. W. B. de Groot: Consulting/advisory role for Amgen, Bayer, Celgene, Roche, Bristol-Myers Squibb, GSK, and Mercck Serono. N. Yamauchi: Advisory role for Chugai Pharma, Ono Pharmaceutical, GlaxoSmithKline, Takeda, AstaZeneca Japan, Boehringer Ingelhein, and Maruhoo. C. Loquast: Advisory board member for Roche, Bristol-Myers Squibb, MSD, and Amgen. L. A. de Pavela: Employee of Novartis Pharma AG; may own stock or stock options. M. Pickard: Employee of Array BioPharma; may own stock or stock options. V. Sandor: Employee/leadership role at Array BioPharma; stock or other ownership of Array BioPharma and Incyte Corp. G. Robert: Consultant for Roche, Novartis, Bristol-Myers Squibb, MSD, and AstraZeneca. K. T. Flaherty: Honoraria from and consulting/advisory role for Novartis and Array BioPharma; research funding from Novartis. All other authors have declared no conflicts of interest.
options in the BRAFv600 melanoma setting. We analysed outcomes in patients (pts) treated with BRAF+MEK1 to characterize pts with rapid progression.

**Methods:** In this multicenter retrospective analysis, 164 consecutive pts affected by BRAFv600 metastatic melanoma and treated with BRAF+MEK1 from February 2012 to April 2017 were included.

**Results:** Overall, 164 patients were enrolled. Baseline LDH was elevated in 68 (41%) pts, baseline number of metastatic organs were 1, 2, 3 and more in 52 (32%), 52 (32%), 29 (18%) and 32 (19%) pts. BRAF1+MEK1 administered were dabrafenib+trametinib in 151 pts and vemurafenib+cobimetinib in 13 pts, and they were administered in first line in 129 (79%) pts. Best response was CR, PR, SD and PD in 27 (16%), 87 (53%), 17 (10%) and 27 (16%) pts. On cutoff date, progression was observed in 104 (66%) pts; 60 (37%) pts still on treatment. mPFS was 9.83 (1.54-7.7) months: significant difference in PFS was shown in pts with normal baseline LDH or high LDH (13.2 vs 6.3 months, p < 0.0001), and in pts with number of metastatic organs lower or higher then 2 (13.4 vs 7 months, p < 0.0001), mOS was 18 (3.61-62.5) months: significant difference in OS was showed in pts with normal baseline LDH or high LDH had (24.7 vs 10 months, p < 0.0006), and in pts with number of metastatic organs lower or higher then 2 (25.9 vs 10 months, p < 0.0003). Among 104 progressed pts, 72 (69%) pts died, mOS after progression was 2.5 months (0.42+ months). Subsequent treatments were administered in 44 (42%) pts. Duration of response (DR) was defined as time from BRAF+MEK1 best response to progression of disease: Significant difference in OS after BRAF+MEK1 progression was observed in pts with DR < 6 months (77 pts - 26%) (2 vs 8.3 months, p < 0.0023) and in pts with number of metastatic organs after progression lower or higher then 2 (4.5 vs 2 months, p < 0.022). Conclusions: BRAF+MEK1 progression during BRAF+MEK1 is a factors that can be useful to identify pts with lower OS after progression, in addiction to known parameters like LDH and baseline number of metastatic organs.

**Legal entity responsible for the study:** IMI

**Funding:**

None

**Disclosure:** R. Marconcini: Received payment for consultancy and honoraria for speaking from Bristol-Myers Squibb, MSD, Roche, Novartis. All other authors have declared no conflicts of interest.

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**1248P Tumor-stroma interactions as a determinant of drug resistance in BRAF-mut melanoma**

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1Medical Oncology, 1. Regina Elena National Cancer Institute, Rome, Italy. 2Department of Research, Diagnostics and Technological Innovation, 3 Regina Elena National Cancer Institute, Rome, Italy. "Of Cutaenous Pathophysiology and Integrated Center of Metabolism Research, San Gallicano Dermatologic Institute, Rome, Italy.

**Background:** In BRAF-mut melanoma combined BRAF+MEK inhibition increases survival; however, pharmacological effects on the genetically "normal" tumor microenvironment (i.e. paradox MAPK activation) may set the stage for the development of drug resistance. Methods: GEP-labeled cutaneous fibroblasts (HFF) were co-cultured with melanoma cells, in the presence or absence of direct cell-cell contact, and response to Dabrafenib (D) and Trametinib (T), alone or combined, was monitored over time. SEMA6A and AXL were preliminarily evaluated as potential mediators of such interactions.

**Results:** HFF significantly protected (60%-100% protection at the lowest two drug concentrations) BRAF-mut M14 melanoma cells from the growth inhibitory activity of D and T, alone or combined; however, combined D+T at the highest concentrations overcame stroma-mediated protection and eliminated both cell populations. Thus, combined BRAF+MEK inhibition resulted in strongly synergistic interactions, as compared to single-agent treatments, only under co-culture conditions (CI 0.6 and 0.2 for M14 and HFF cells, respectively). Protective melanoma/stroma interactions were mediated by direct cell-cell contact, as co-cultures in trans-well Boyden chambers or isolated cultures of melanoma cells co-cultured and treated with combined D+T were unable to reach the same protection levels. The highest D+T concentrations used (2000-20,000 U/mL) for MAPK inhibition, 100% cell viability was reached after 72 hours. SEMA6A and AXL expression in a panel of melanoma cell lines were inversely correlated, moreover, in cell lines derived by primary and cutaneous metastases of the same patient, AXL expression was upregulated at the mRNA and protein levels in cells derived from metastatic lesions.

**Conclusions:** Tumor-stroma interactions protect BRAF-mut melanomas from BRAF inhibition, such functional protection is mediated by cell-cell contact. SEMA6A and AXL are possible mediators of this interaction and their reciprocal relationships are being studied in melanoma cell line models and clinical series.

**Legal entity responsible for the study:** Regina Elena Cancer Institute- San Gallicano Dermatologic Institute

**Funding:** AIRC (18622-14362-9979)

**Disclosure:** All authors have declared no conflicts of interest.
and 71% remained on the NIVO portion of the NIVO + IPI regimen. Permanent discontinuation of treatment prior to completing planned courses of therapy was relatively infrequent (IPI: 16%, NIVO: 26%, NIVO + IPI: 19%), possibly reflecting improved experience in toxicity assessment and management.

**Conclusions:** Within this real-world cohort, a minority of pts discontinued NIVO or NIVO + IPI by 6 months. This research sheds light on current treatment patterns for IPI, NIVO, and their combination.

**Clinical trial identification:** CA209-983

**Legal entity responsible for the study:** Bristol-Myers Squibb

**Funding:** Bristol-Myers Squibb

**Disclosure:** A. Tarhini: Served as a consultant or advisor for Bristol-Myers Squibb; received institutional research funding from Amgen, Bristol-Myers Squibb, Incyte, MSD, Novartis, and Prometheus Laboratories. C. Macauley: Employed by Medical Data Analytics, where she provides study design and data collection. C. Atzinger: Received personal fees from Bristol-Myers Squibb; employee of Pharmerit International. K. Gupta-Singh: Employee of Bristol-Myers Squibb and has stock/ownership in Bristol-Myers Squibb. C. Solem: Institution received consulting fees from Bristol-Myers Squibb to conduct this research. S. Rao: Employed by Bristol-Myers Squibb and has stock/ownership in Bristol-Myers Squibb.

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### 1251P

**Baseline neutrophil-to-lymphocyte ratio and its values monitored over time is associated with outcome of metastatic melanoma patients treated with immunotherapy**

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**Background:** Neutrophil-to-lymphocyte ratio (N/L) was shown to be prognostic in several solid malignancies. There are limited data about changes of N/L ratios during immunotherapy. The aim of the study was to assess a clinical value of this ratio and its association with tumour response in patients with advanced melanoma.

**Methods:** Between June 2011 and March 2017, 308 patients with metastatic/unresectable melanoma were included to the analysis. Patients age was 58.4 ± 17.3 years, 43 cases had brain metastases. BRAF mutation was present in 107 cases, and 98 patients had positive mutation received targeted therapies with BRAF+/ MEK followed by ipilimumab and/or anti-PD1 therapy. Patients with BRAF negative received immunotherapy (pembrolizumab or nivolumab with/without ipilimumab). In all patients the N/L ratio was assessed at the baseline and monitored during treatment until disease progression or last observation. The cut off for ratio N/L was set at 3. Logistic GEE and Kaplan-Meier survival probability estimation were used for analysis.

**Results:** N/L ratio ≥ 3 at baseline was significantly associated with poorer overall survival (OS) (p < 0.001 in log-rank test). Median overall survival time was 25.8 months (95%CI 20.4-31.2) for N/L ratio < 3 vs. 14.0 months (95%CI 10.7-17.3) for N/L ratio ≥ 3. In repeated measurements analysis, increased N/L ratio was significantly associated the confirmed disease progression, both in univariate random effect model (p < 0.001) and multivariate model adjusted for age, gender, presence of BRAF mutation and LDH > URL (p < 0.001). N/L ratio in all 6 patient who had pseudo-progression on immunotherapy was not elevated over time.

**Conclusions:** Our results confirm the usefulness of N/L ratio as a prognostic and predictive marker in patients with metastatic melanoma, and monitoring of the N/L ratio over immunotherapy may be helpful for assessment of the disease progression, response, as well as pseudoprogression, thus likely contribute to an optimization of treatment and resource allocation in patients with metastatic melanoma.

**Legal entity responsible for the study:** Maria Skłodowska-Curie Institute and Oncology Center, Warsaw, Poland

**Funding:** None

**Disclosure:** B. Cybulska-Stopa, H. Kośela-Paterczyk: Personal fees for lectures from Novartis, Roche, Bristol-Myers Squibb, MSD. K. Kiełak: Personal fees for lectures from Novartis, Roche, Bristol-Myers Squibb and MSD. P. Rutkowski: Reports personal fees from Novartis, Bristol-Myers Squibb, Roche, MSD, GSK, Amgen - lecture honoraria and membership of Advisory outside the submitted work. All other authors have declared no conflicts of interest.
Characteristics of metastatic melanoma (MM) patients with leptomeningeal disease (LMD) and survival of > 1 year

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Background: Several studies have demonstrated that the presence of LMD correlates with very short overall survival (OS) in metastatic melanoma patients (pts). However, a subset of pts have OS > 12 months (mts). We reviewed the outcomes of a large cohort of pts with LMD to identify predictors of improved outcomes.

Methods: The clinical features, treatments, and OS of MM pts diagnosed with LMD by CSF cytology and/or radiographic findings from 2000 to 2015 were reviewed. Landmark Cox proportional hazard regression models were used to identify factors significantly associated with OS > 12 mts.

Results: 178 pts with LMD were identified. For these, median age at diagnosis (dx) was 51.2 years. 62% were male, 75% pts had a performance status of ECOG 0-1, 39% had elevated LDH, extracranial disease present in 73% and concurrent brain metastasis in 77%, 36% of pts were tested for BRAF mutation, and 37% (of those tested) were positive. 65% of pts had CSF analysis done, but 49% of those had positive cytology. Neurological deficits were reported in 49%. Median OS from LMD diagnosis was 4.72 mts (95% CI: 3.12-5.55), and 12-, 36-, and 60-mts cumulative OS was 0.22 (95% CI: 0.163-0.290), 0.11 (95% CI: 0.096-0.169), and 0.09 (95% CI: 0.054-0.131), respectively. Compared to those who died within 3 mts, pts who lived longer than 12 mts (n = 36) were more likely to have: ECOG of 0 (57.1% versus 15.3%), previous surgery (52.0% versus 25.3%), and CSF cytology positive at dx (41.2% versus 33.3%), intracranial therapy (69.4% versus 21.6%), and chemotherapy (61.1% versus 37.8%). and were less likely to have neurological deficits (27.8% versus 62.7%), previous systemic therapy (63.9% versus 80.0%), and LDH above normal (94.0% versus 45.9%). Positive CSF cytology (HR = 0.306, 95% CI 1.02-9.17) and concomitant systemic disease (HR = 2.65, 95% CI 1.03-6.82) were associated with significantly shorter OS.

Conclusions: Long term survival in MM pts with LMD is rare, but possible. Features significantly associated with OS may help strengthen the design and interpretation of future trials for pts with LMD.

Legal entity responsible for the study: Isabella C. Ginestrè

Disclosure: All authors have declared no conflicts of interest.

Tolerance and outcomes of stereotactic radiosurgery combined with an anti-PD1 (pembrolizumab) for melanoma brain metastases


Background: Anti-PD1 antibodies are currently the first-line treatment for patients with metastatic BRAF wild-type melanoma, alone or combined with the anti-CTLA4 mAb, ipilimumab. To date, data on safety and outcomes of the patients treated with the anti-PD1 mAb pembrolizumab (PB) or nivolumab combined with stereotactic radiosurgery (SRS) for melanoma brain metastases (MBM) are lacking.

Methods: Patients with MBM treated with PB combined with SRS between 2012 and 2015 were retrospectively reviewed. The primary endpoint was neurotoxicity. The secondary endpoints were local control, distant intracranial control and overall survival (OS).

Results: Among 74 patients with MBM treated with SRS, 25 patients with a total of 38 MBM treated with PB combined with SRS within 6 months were included. Radiocrosses, occurring within a median time of 6 months, was observed in four metastases (6.8%) in four different patients. No significant other SRS-related adverse event had been reported. After a median follow-up of 8.4 months, local control had been achieved in 46 metastases (80%). The median time to local progression was 2 months. Perilesional oedema and intratumoural haemorrhage appearing or increasing after SRS were mostly associated with local progression (P < 0.001). Median OS was 15.3 months (95% CI: 11.4-26.2). The timing between SRS and PB administration did not seem to influence radiocrosses, intracranial control or OS.

Conclusions: SRS combined with PB was well tolerated and achieved high local control as recently described with SRS and nivolumab. Prolonged OS were achieved compared to that currently yielded with recommended treatments. Prospective studies are required to confirm these results and define the best timing between SRS and PB for the management of MBM.

Legal entity responsible for the study: Caroline Robert, Gustave Roussy

Funding: None

Disclosure: All authors have declared no conflicts of interest.
A Phase II, Randomised, Open Label Study of Neoadjuvant Pembrolizumab with/without Dabrafenib and Trametinib (D+T) in BRAF V600 Mutant Resectable Stage IIIb/C Melanoma (NeoTRIO Trial)


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Background: BRAF targeted and CTLA-4/PD-1 immunotherapies have high response rates and improve survival for patients (pts) with metastatic melanoma, however, most still die of this disease. It is hypothesised the activated cytotoxic T cell infiltrate that occurs early during treatment with BRAF/MEK inhibitors is potentiated by adding checkpoint inhibitors, resulting in improved response and survival. While trials combining BRAF/MEK inhibitors and anti-PD-1/PD-1 antibodies are underway in the meta-static setting, the neoadjuvant setting provides an opportunity to test different treatment schedules in small cohorts of pts. Tissue and blood biomarkers can be drawn at several time points and correlated to pathological endpoints to explore mechanisms of response, biomarkers of efficacy, and to select the best schedules to take forward to larger-scale trials.

Trial design: Eligible pts with BRAF V600 mutant, stage IIIb/C, resectable and measurable (RECIST 1.1) metastatic melanoma are evenly assigned to 2 cohorts (n = 60). All pts undergo complete macroscopic resection (RES) at week 12 and receive neoadjuvant therapy for 12 weeks preceding RES, followed by 40 weeks of adjuvant therapy. Cohort 1 receive sequential therapy with D+T for 2 weeks, followed by 4 pembrolizumab (pembro) doses until week 12, and 3 pembrolizumab (pembro) doses after initial CR may discontinue pembrolizumab. Cohort 2 receive concurrent D+T for 2 weeks before RES. Primary end points are safety and ORR; secondary endpoints include RECIST response, metabolic response, OS, RFS, safety/toxicity, surgical outcomes, quality of life, as well as biomarker analysis.

Clinical trial identification: NCT02889821

Legal entity responsible for the study: Melanoma Institute Australia

Funding: Merck Sharp & Dohme

Disclosure: All authors have declared no conflicts of interest.

KEYNOTE-029: Phase I/II randomized study of pembrolizumab (pembro) plus 2 dose regimens of ipilimumab (ipi) for advanced melanoma


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Background: Continuous combinations of targeted therapy (TT), e.g. BRAFi + MEKi, with immunotherapy (IT), e.g. CTLA-4 or PD-1 blockade are currently tested in several phase I/II trials with the aim to improve response rate and response duration in melanoma patients with a BRAFV600 mutation. However, high toxicity rates have been observed, revealing PD-1 blockade currently being the only possible combination partner for TT. Recently we have published preclinical data, showing that short-time TT induces strong T cell infiltration and is synergistic with PD-1 blockade. Analysis of biopsies of patients during TT indicates that long-term TT might be counterproductive, as T cell infiltration decreases in some patients already beyond 2 weeks. This raises the question which time period of MAPK pathway inhibition is optimal for combination with anti-PD-1/anti-CTLA-4 monotherapy, comparing PEM monotherapy with combination schemes of intermittent/short-term BRAFi + MEKi plus PEM. The primary objective is to explore feasibility, safety and the immune-activating capacity of the different regimens.

Phase 2 Study Comparing Pembrolizumab with Intermittent/short-term dual MAPK pathway inhibition plus Pembrolizumab (PEM) in patients harboring the BRAFV600 mutation (IMPemBra Trial)

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Background: Continuous combinations of targeted therapy (TT), e.g. BRAFi + MEKi, with immunotherapy (IT), e.g. CTLA-4 or PD-1 blockade are currently tested in several phase I/II trials with the aim to improve response rate and response duration in melanoma patients with a BRAFV600 mutation. However, high toxicity rates have been observed, revealing PD-1 blockade currently being the only possible combination partner for TT. Recently we have published preclinical data, showing that short-time TT induces strong T cell infiltration and is synergistic with PD-1 blockade. Analysis of biopsies of patients during TT indicates that long-term TT might be counterproductive, as T cell infiltration decreases in some patients already beyond 2 weeks. This raises the question which time period of MAPK pathway inhibition is optimal for combination with anti-PD-1/anti-CTLA-4 monotherapy, comparing PEM monotherapy with combination schemes of intermittent/short-term BRAFi + MEKi plus PEM. The primary objective is to explore feasibility, safety and the immune-activating capacity of the different regimens.
Trial design: Stage IV BRAF V600E/K mutation positive melanoma patients, naive for IT and TT, will start treatment with PEM 200mg q4w. After 6wks the patients will be randomized (stratified according their LDH level) to continue PEM for up to 2yrs (cohort 1), one of the experimental cohorts receiving either dabrafenib 150mg, BID + trametinib 2mg QD two times intermittent for 1wks (cohort 2), two times intermittent for 2wks (cohort 3), or continuous for 6wks (cohort 4). All cohorts continue afterwards with PEM for up to 2yrs. Each cohort will consist of 8 patients. Primary end points are SUCBRs and adherence to the study timeline, the intra-patient variation in intratumoral CD8+ T cells and the percentage PD1 + CD8+ T cells in the peripheral blood. Tumor biopsies and blood samples including PBMCs are taken at baseline, wk 6, 9, 12, 18 and in case of progression. Secondary end points are objective response rate and progression free survival. Enrollment started in May 2016, 11 patients have been included so far.

Clinical trial identification: NCT02653337

Legal entity responsible for the study: NCI-AVL

Funding: MSD

Disclosure: J.V. Thielen: Advisory board: MSD and Bristol-Myers Squib. J.B. Haanen: Advisory role: Bristol-Myers Squib. MSD, Pfizer, Roche, Novartis, Neon Therapeutics Research Institute: Bristol-Myers Squib. MSD, GSK. C.U. Blank: Advisory boards: Bristol-Myers Squib, MSD, Novartis, GSK, Pfizer, Lilly. Roche Research grants: Bristol-Myers Squib, Novartis. All other authors have declared no conflicts of interest.

1259TIP

A randomized, double-blind, placebo-controlled, phase III study comparing the combination of PDR001, dabrafenib and trametinib versus placebo, dabrafenib and trametinib in previously untreated patients with unresectable or metastatic BRAF V600-mutant melanoma (COMBI-i)


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Background: Checkpoint inhibitor and targeted therapies are both important tools in the management of BRAF V600-mutated unresectable or metastatic melanoma. Although these therapies have improved responses and overall survival, many patients still progress and die from this disease. Thus, additional treatment strategies are needed to improve durability of responses and related long-term outcomes in these patients. Based on preclinical and preliminary clinical data, BRAF and MEK inhibitors can reverse the oncogenic BRAF-induced immune-suppressive phenotype through enhanced melanoma antigen expression and enhanced tumor antigen-specific T lymphocyte recognition in vivo. These data suggest that there is potential clinical benefit in combining dabrafenib and trametinib with checkpoint inhibitor therapy.

Trial design: The 3-part COMBI-i phase 3 study (NCT02967692) will evaluate the safety and efficacy of PDR001, an investigational anti-programmed death 1 antibody in combination with dabrafenib and trametinib in previously untreated patients with BRAF V600-mutated unresectable or metastatic melanoma. In part 1, a safety run-in will establish the recommended phase 3 regimen (RP3R) for use in part 3 using an adaptive Bayesian logistic regression model. In part 2, tissue and blood samples from the biomarker cohort will be used to characterize baseline immune markers and explore potential immune marker modulation by the triple therapy. Part 3 is the randomized, double-blind, placebo-controlled portion that will open once the RP3R has been determined. Approximately 500 patients will be randomized 1:1 to receive either PDR001 in combination with dabrafenib and trametinib or placebo in combination with dabrafenib and trametinib, with randomization stratified based on Eastern Cooperative Oncology Group performance status and lactate dehydrogenase level. The primary endpoint will be progression-free survival per investigator’s assessment according to RECIST v1.1. Overall survival will be a key secondary endpoint.

1260TIP

Late physical, psychological and social consequences of ipilimumab treatment in advanced melanoma


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Medical Oncology, Medical Centre Leeuwarden, Leeuwarden, Netherlands,
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Oncology, Bristol-Myers Squibb, Utrecht, Netherlands,
Oncology, Bristol-Myers Squibb, Cancer Institute, Amsterdam, Netherlands

Background: After the introduction of ipilimumab, an anti-CTLA-4 monoclonal antibody, durable, long term survival has been observed in patients with refractory metastatic melanoma patients. Since ipilimumab is a relatively novel drug there are limited data on the long-term physical, psychological, and social functioning of these patients. This study will evaluate the long-term physical and psychosocial well-being and the information needs of advanced melanoma survivors who have been treated with ipilimumab.

Legal entity responsible for the study: Novartis Pharmaceuticals Corporation

Funding: Novartis Pharmaceuticals Corporation

Disclosure: E. Grgic: Employment: Novartis Stock or Other Ownership: Amgen Inc, A.M. Arance Fernandez: Honoraria, Consulting/Advisory Role, and Speakers Bureau: Roche, Bristol-Myers Squibb, MSD, Pfizer, Roche, Novartis, neon Therapeutics Research Institute: Bristol-Myers Squib, MSD, Novartis, GSK, Pfizer, Lilly. Roche Research grants: Bristol-Myers Squib, Novartis. All other authors have declared no conflicts of interest.

Clinical trial identification: NCT02967692 First received: November 16, 2016
Trial design: This is a prospectively enrolling, multicentre cohort study. Objectives: To assess health-related quality of life (HRQoL), anxiety, depression, fatigue, fear of cancer recurrence, sexual health and generic health status in patients with advanced melanoma who have survived at least 2 years after ipilimumab treatment (without subsequent other systemic therapies) as compared with healthy controls, and to describe the melanoma-specific HRQoL, impact of cancer, social functioning and information needs in patients with advanced melanoma who have survived at least 2 years after ipilimumab treatment. Patients and healthy control population: Patients with advanced (stage IV or unresectable stage III) melanoma who survived at least 2 years and were treated with ipilimumab between 2011 and 2015 in 14 hospitals in the Netherlands are included. The patient population consists of 3 treatment groups based on time since ipilimumab treatment: 24 to < 36 months, ≥ 36 to < 48 months and ≥ 48 months post-ipilimumab treatment. The healthy control population will be selected from Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship (PROFILES). PROFILES contains a reference cohort of more than 2000 healthy individuals and is designed to be representative of the Dutch-speaking population in the Netherlands. Measurements: The primary and secondary study outcomes will be measured by questionnaires, at 3 time-points in patients 24 to < 36 months and at 1 time-point in patients ≥ 36 months post-ipilimumab treatment. The primary outcome, HRQoL, will be assessed with the European Organisation for Research and Treatment of Cancer quality of life questionnaire-C30 (EORTC QLQ-C30).

Clinical trial identification: Date of release: November 2016

Legal entity responsible for the study: Netherlands Cancer Institute

Funding: Bristol-Myers Squibb

Disclosure: A.H. Boekhout: Employee of Bristol-Myers Squibb. M. Lee, KJM Janssen: Employee of and receiving stock from Bristol-Myers Squibb. During the conduct of the study. All other authors have declared no conflicts of interest.
Background: In contrast to general belief, a substantial part of the human coding transcriptome is abundantly present in the blood as extracellular mRNA, ready to be exploited. It is well known that cancer cells actively and passively release RNA cargo into circulation and their detection may inform on the patient disease status.

Methods: We developed and applied a probe based RNA capture sequencing method as a sensitive RNA sequencing workflow to study thousands of transcripts in cell-free RNA from cancer patients’ plasma. The method is based on exome-style enrichment of a randomly primed cDNA library with preservation of strandedness information. More than one million capture probes target 21,000 human messenger RNA and 60,000 human long non-coding RNA genes. Apart from RNA abundance profiling, this type of data can also be used to detect structural RNA variants, such as somatic mutations, fusion genes, and RNA editing events, all known to play an important role in cancer.

Results: On average, between 6000-10,000 RNA genes are reproducibly detected in 0.2 ml of plasma. Detection and coverage sensitivity is greatly increased by using larger plasma volumes and improved adaptation strategy as also observed correlation between number of platelets in plasma and detected genes and variants, in line with their tumor-educated nature. Our benchmarked RNA variant pipeline identifies thousands of germline and somatic variants in circulating mRNA. A dedicated titration experiment in which plasma from cancer and healthy individuals were mixed in known ratios demonstrates excellent quantitative performance. Pronounced RNA abundance differences and enriched pathways are observed between cancer types and during treatment. The RNA capture sequencing also works on other body fluids, such as urine and serum, and simultaneous targeting of mRNA and IncRNA provides substantial enrichment of otherwise low-abundant IncRNAs.

Conclusions: RNA capture sequencing of liquid biopsies is a promising new application to support precision oncology and is expected to enhance therapy stratification, treatment response monitoring and early detection of relapse.

Legal entity responsible for the study: Biogazelle and Ghent University

Funding: Biogazelle, Illumina

Disclosure: J. Vandemoorpe. Apart from professorship at Ghent University, co-founder and part-time CSO at Biogazelle, a Ghent University spin-off company.

1262P Use of droplet digital PCR for quantitative and automatic analysis of the HER2 status in breast cancer patients

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Background: Digital polymerase chain reaction (dPCR) has been used to yield an absolute measure of nucleic acid concentrations. Recently, a new method referred to as droplet digital PCR (ddPCR) has gained attention as a more precise and less subjective assay to quantify DNA amplification. We demonstrated the usefulness of ddPCR to determine HER2 gene amplification of breast cancer.

Methods: In this study, we used ddPCR to measure the HER2 gene copy number in clinical formalin-fixed paraffin-embedded samples of 41 primary breast cancer patients. To improve the accuracy of ddPCR analysis, we also estimated the tumour content ratio (TCR), the ratio of tumour cell count per section, for each sample.

Results: Our determination method for HER2 gene amplification using the ddPCR ratio (ERBB2:CHC-7 cent copy number ratio) correlated with the TCR showed high consistency with the conventionally defined HER2 gene status according to ASCO-CAP (American Society of Clinical Oncology/Collage of American Pathologists) guidelines (P < 0.0001, Fisher’s exact test). The equivocal area was established by adopting 89% confidence intervals obtained by cell line assays, which made it possible to identify all conventionally HER2-positive cases with our method. In addition, we succeeded in automating a major part of the process from DNA extraction to determination of HER2 gene status.

Conclusions: The introduction of ddPCR to determine the HER2 gene status in breast cancer is feasible for use in clinical practice and might complement or even replace conventional methods of examination in the future.

Legal entity responsible for the study: The University of Tokyo

Funding: None

Disclosure: All authors have declared no conflicts of interest.

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Background: Peripheral blood circulating tumor DNA (ctDNA) and tumor tissue next-generation sequencing (NGS) is routinely performed to guide therapy in cancer patients. However, little is known about the concordance or discordance between commercially available tissue genomics testing panels and ctDNA. The aim of our study was to assess concordance between matched cancer tissue genomics and blood based ctDNA panels. When this testing was done within 90 days the concordance increased to 21% (n = 6/28).

Methods: Tissue genomics analysis was performed with Paradigm® (n = 17)/Cares® (n = 11) and ctDNA was analyzed with Guardant360® (n = 28). Samples included, non-small cell lung cancer (n = 10), small cell lung cancer (n = 4), colorectal cancer (n = 3), hepatocellular carcinoma (n = 2), intrathoracic cholangiocarcinoma (n = 1), pancreaticobiliary adenocarcinoma (n = 3), esophageal adenocarcinoma (n = 2) and gastric adenocarcinoma (n = 1).

Results: We identified 6 (21%) patients with at least one gene mutation that was detected by both tissue genomic and ctDNA analysis. Total number of gene mutations identified in 28 patients were 106, but only 8 (7.5%) were detected by both tissue genomic and ctDNA analysis. Total number of gene mutations detected by both tissue and ctDNA panels. When this testing was done within 90 days the concordance increased to 10.26%

Table: Table 1265P

<table>
<thead>
<tr>
<th>Patients with at least one mutation detected</th>
<th>21% (n = 6/28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>by both platforms</td>
<td>7.54% (n = 8/106)</td>
</tr>
<tr>
<td>Mutations detectable by both platforms</td>
<td>10.20% (n = 5/49)</td>
</tr>
<tr>
<td>if interval between tissue and blood</td>
<td></td>
</tr>
<tr>
<td>collection &lt;90 days</td>
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</table>

Conclusions: We identified significant discordance between tissue and ctDNA mutational profiles in lung and GI cancers. Therefore, the results from NGS platforms should be interpreted with extreme caution. Our analysis reveals that these platforms should not be used interchangeably. The discordance rate may be due to tissue heterogeneity and/or spatial and temporal clonal evolution. Standardization of the sequencing techniques and education of practicing oncologists about the limitations of liquid biopsies needs to be highlighted.

Legal entity responsible for the study: Saint Luke’s Health System
Funding: None
Disclosure: J. Subramanian - Paradigm Advisory board. All other authors have declared no conflicts of interest.
showed no statistically significant difference in PFS between MTA and control arm. The addition of functional information on identified mutations and their response to MTA’s may improve treatment outcomes.

Methods: The molecular profile of 20 pts treated with a MTA in the trial was analyzed in the NovelluRx Functional Annotation for Cancer Treatment (FACT), a functional mutational analysis platform, to reveal activated signaling pathways and measure the activity of these mutations in the presence of the MTA’s administered in the trial. The results of FACT were used to stratify the pts into responders and non-responders.

Results: We uncovered the functional landscape in 12 of the 20 pts in the analyzed group. In the remaining 8 pts, no relevant mutational alterations were identified. This analysis provided experimental evidence to the oncogenic activity of the mutations and of the combination of mutations identified in the pts. Furthermore, the response of these pts’ mutations to the MTA’s used was measured in-vitro, blinded to the actual clinical results. Each patient was then assigned as either a responsive or non-responsive. When the results were used to stratify the pts’ PFS data, positive predictive values had a median PFS of 5.8 months vs. 1.7 months in the negative group (P = 0.03 in a non-parametric test).

Conclusions: This analysis shows the predictive power of a new and innovative method for characterization of pts molecular profiles and their in-vitro response to MTA’s. The abundance of mutations classified as VUS and multiple mutations in different genes reveals the complexity in assigning the optimal MTA and the necessity of a functional assay to predict efficacy. Furthermore, the functional analysis provided results correlated into responsive and pts with no molecular basis for a benefit in MTA treatment. Importantly, the hypothesis driving the SHIVA01 trial proved positive by the addition of the functional interpretation of the mutational data.

Legal entity responsible for the study: Instituto Curie, Paris, France

Funding: None

Disclosure: G. Taric, O. Edelheit, Z. Barbash, M. Vidne, B. Mirón: A full time employee of NovelluRx. All other authors have declared no conflicts of interest.

Integrative multi-platform meta-analysis of gene expression profiles in pancreatic ductal adenocarcinoma patients for identifying novel diagnostic biomarkers


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Background: Applying differentially expressed genes (DEGs) to identify feasible biomarkers in diseases can be a hard task when working with heterogeneous datasets. Expression data are strongly influenced by technology, sample preparation processes, and/or labeling methods. The proliferation of different microarray platforms for measuring gene expression increases the need to develop models able to compare their results, especially when different technologies can lead to signal values that vary greatly. Integrative meta-analysis can significantly improve the reliability and robustness of DEG detection. The objective of this work was to develop an integrative approach for identifying potential cancer biomarkers by integrating gene expression data from two different platforms. Pancreatic ductal adenocarcinoma (PDAC), where there is an urgent need to find new biomarkers due to its late diagnosis, is an ideal candidate for testing this technology.

Methods: Expression data from two different datasets, namely Affymetrix and Illumina (18 and 36 PDAC patients, respectively), as well as from 18 healthy controls, was used for this study. A meta-analysis based on an empirical Bayesian methodology (ComBat) was then proposed to integrate these datasets. DEGs were finally identified from the integrated data by using the statistical programming language R.

Results: After our integrative meta-analysis, 5 genes were commonly identified within these datasets. 1269P 3D Cultured Tumour from Patients to Predict Treatment Response

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Background: Treatment selection for cancer patients is still a challenge. Average response rates for standard chemotherapy are low due to a lack of predictive markers. Genetic approaches to improve treatment efficacy have not yet delivered solutions for the day-to-day clinic. Functional testing of 3D cultures of patient tumour biopsies has the potential to identify tumours that are sensitive to standard drugs, search for alternative drugs when treatment options appear exhausted, and prevent overtreatment. Our technology based on image analysis of 3D tumour cultures accommodates accurate evaluation of drug sensitivity with small amounts of heterogeneous tumour material. We aim to validate our methods, and develop diagnostics to predict drug response for cancer patients.

Methods: 3D cultures embedded in a protein-rich hydrogel are generated from tumour biopsies, and exposed to standard-of-care therapies, targeted therapies and drug combinations: An automated high content screening platform measures cell and tissue morphology, and reports responses such as tumour cell killing, growth arrest and local invasion. Per tumour type and drug, morphological features are selected as standard read-outs for the response. Proof of Concept (PoC) trials have been initiated to compare drug sensitivity of tumour cultures in treatment responses observed.

Results: We present results of PoC experiments showing drug sensitivity in 3D cultures of fresh and cryopreserved tumour material of gastric, endometrial, cervical, and ovarian cancer patients. Standard-of-care therapies were tested and results were compared per drug (combination). Differentiated drug responses are identified for treatment schedules including platinum-based drugs, taxanes, antracyclines, 5-FU. In addition, responses to drugs that are not (yet) considered standard of care (PARP inhibitors) were measured.

Conclusions: Our technology enables drug sensitivity testing in 3D cultures of tumour tissues. This allows patient-specific treatment responses to developmental and standard-of-care drugs to be determined. Ongoing PoC trials will reveal the correlation of our in vitro test with treatment responses in the clinic.

Legal entity responsible for the study: VitroScan B.V.

Funding: VitroScan B.V.

Disclosure: All authors have declared no conflicts of interest.

5-ALA administration for photodynamic diagnosis of peritoneal metastases due to advanced gastric cancer: A randomised, double-blind, multicentre phase I/I study


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Background: For advanced gastric cancer, diagnosis of peritoneal dissemination is mandatory prior to the decision of therapy; therefore, staging laparoscopy (SL) has gained wider clinical acceptance. We have reported the efficacy of 5-ALA with photodynamic diagnosis (PDD) using 5-aminolevulinic acid (5-ALA). In this study, the safety and effectiveness of oral administration of 5-ALA PDD compared with that of conventional white-light laparoscopic diagnosis is assessed in a phase I/I study. This research also used a randomised double-blind comparison to explore the optimum dose of 5-ALA to be followed by a confirmatory study.

Methods: Subjects were patients with type 3 or 4 gastric cancer. A total of 20 or 40 mg/ kg 5-ALA was administered orally 180–300 minutes before SL. The primary endpoint was safety; the secondary endpoints were sensitivity, specificity, positive predictive value, negative predictive value, and the proportion of patients with peritoneal dissemination.

Results: Thirty-one patients, comprising 19 men and 12 women, were enrolled. Fourteen patients were allocated to the 20 mg/kg group and 17 to the 40 mg/kg group. The median age was 70 years. The proportions of adverse events were 53.8% and 41.2% in the 20 and 40 mg/kg groups, respectively. Hypotension was noted as serious adverse event in 1 patient. The sensitivities of PDD in the 20 and 40 mg/kg groups were higher (95.7% and 100%, respectively) than those of conventional diagnosis (73.9% and 67.8%) (P = 0.0625 and P = 0.0313). In terms of precision, the evaluation values of diagnosis through conventional imaging compared with PDD were as follows: sensitivity, 83.5% vs. 98.6%, specificity, 75.5% vs. 38.8%, positive predictive value, 82.2% vs. 69.6%, and negative predictive value, 75.5% vs. 95.0%, respectively. In addition, one more patient was found positive for dissemination via PDD.
Conclusions: This investigator-initiated clinical trial confirmed the safety and effectiveness of S-ALA administration in PDD for peritoneal metastases in gastric cancer. Results indicated that both doses of S-ALA may be clinically applicable. Thus, we are now conducting a confirmatory study to apply for pharmaceutical approval of S-ALA.

Clinical trial identification: JMA-IA00225

Legal entity responsible for the study: Prof. Yuichiro Doki

Funding: This work was supported by the clinical trial promotion pro-gra subsidied by the Japan Medical Association with the Ministry of Health, Labour and Welfare Research Grant

Disclosure: All authors have declared no conflicts of interest.

Diagnostic performance of dedicated breast PET scanner with a ring detector

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Background: Dedicated breast positron emission tomography scanners (dbPET) have been developed to make possible higher spatial resolution and sensitivity. The purpose of this study was to investigate the diagnostic performance of dbPET with an O-shaped detector in patients with known breast cancer.

Methods: A total of 82 female patients diagnosed with breast cancer consented to participate in this study (84 lesions: 10 ductal carcinomas in situ (DCIS), 74 invasive cancers). All patients underwent a WB-PET/MRI using Biograph mMR (Siemens Healthcare): approximately 80 minutes after fluorine-18 fluoro-deoxyglucose (18F-FDG; 3.0MBq/kg) injection, followed by dbPET using Dedicated Breast PET System Elanmate (Sharpz, Kyoto, Japan) which required 5 minutes per breast.

Results: The overall imaging sensitivities of dbPET and WB-PET/MRI were 89% (75/84) and 87% (74/84) respectively. The sensitivities excluding 5 lesions which were outside the side of view dbPET were 95% (70/73) and 89% (69/77) respectively. The standardized uptake values (SUV) of dbPET (SUVmax mean 1.3, range 1.64-41.6) and WB-PET/MRI (SUVmax mean 5.71, range 1.15-13.3) showed correlation with nuclear grade (50% Spearman’s rank-correlation coefficient r = 0.507, p < 0.001). The sensitivities for DCIS were 90% (9/10), 60% (6/10) respectively. The sensitivities for invasive cancers with 0.3-0.9cm, 1cm, 5cm, and 5cm+ were 67% (12/18), 78% (21/27), 57% (12/21) respectively. We observed six lesions (three high grade DCIS (1.7 cm - 5cm), three high grade invasive cancers with 0.3-0.9cm) that were only detected by dbPET. On the contrary, four lesions could not be detected by either modality (low grade DCIS, invasive lobular carcinoma 2cm, low grade invasive ductal carcinoma with 0.6cm).

Conclusions: Both dbPET and WB-PET/MRI showed high imaging sensitivity, but dbPET has significantly higher sensitivity to high grade DCIS and invasive lesions up to 1cm. This level of diagnostic performance could help to detect early stage cancers as part of breast screening.

Clinical trial identification: We have registered this trial at UMIN (University Hospital Medical Information network): UMIN1190002277 [https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi] Release date: 02 May 2017

Legal entity responsible for the study: Japan

Funding: Shimadzu corporation

Disclosure: All authors have declared no conflicts of interest.

Results of the phase III IFCT-0302 trial assessing minimal versus CT-scan-based follow-up for completely resected non-small cell lung cancer (NSCLC)

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Conclusions: Several guidelines recommend a follow-up based on clinic visits and chest CT-scan for completely resected NSCLC. However, evidence to support these recommendations is poor, in the absence of randomized data. The IFCT-0302 trial is a randomized multicenter trial which compared two follow-up programs for completely resected stage II, IIIa and T4 (pulmonary nodules in the same lobe) N0-2 NSCLC (TNM 6th edition).

Methods: In the control arm (arm 1), follow-up consisted of clinical examination and chest X-ray (CXR). In the experimental arm (arm 2), patients underwent clinical examination, CXR, thoraco-abdominal CT-scan (CT) plus bronchoscopy (optional for adeno carcinomas). In both arms, procedures were repeated every 6 months after randomization during the first 2 years, and yearly until 5 years. Supplementary procedures were allowed in case of symptoms. The primary endpoint was overall survival (OS).

Results: Between January 2005 and November 2012, 1775 patients were randomized (arm 1: 888; arm 2: 887). Patient characteristics were well-balanced between the two arms: males 76.3%, median age 63 years (range: 34-88), squamous and large cell carcinomas 39.5%, stage IIB 18.1%, stage II 13.7%, stage III 18.3%, lobectomy or bilobectomy 86.6%, pre- and/or post-operative radiotherapy 8.7%, and pre- and post-operative chemotherapy 4.7%. Median follow-up was 8.7 years (95% CI: 8.5-9). OS was not significantly different between arms (HR = 0.92, 95% CI: 0.8-1.07; p = 0.27). Median OS was 8.2 years (95% CI: 7.4-9.6) and 10.3 years (95% CI: 8.5-10.6) in arms 1 and 2, respectively. Three-year disease-free survival rates were 63.3% (95%CI: 60.2%-66.5%), and 60.2% (95% CI: 57.0%-63.4%), respectively. Eight-year OS rates were 51.1% (95% CI: 47.2%-55.1%) and 55.6% (95% CI: 51.7%-59.4%) respectively.

Conclusions: The IFCT-0302 trial is the first randomized study of follow-up in resected NSCLC. The primary endpoint was not met. A longer follow-up is necessary not to miss a potential long-term OS benefit of CT-scan-based surveillance.

Clinical trial identification: NCT00198341

Legal entity responsible for the study: Intergroupe Francophone de Cancérologie Thoracique (IFCT)

Funding: Ministère de la Santé (PHRC), Fondation de France, Laboratoire Lilly

Disclosure: E. Quois: Non-financial support from AMGEN, Pfizer, BMS. Personal fees from Abbvie, Clovis and Lilly. Personal fees and non-financial support from Boehringer Ingelheim. All other authors have declared no conflicts of interest.
The analyses revealed the prognostic value of increased relapse-free survival (RFS, 19.1 vs NR months, p = 0.029). The multivariate analysis (including clinico-pathological and analytical variables) showed that this signature has independent prognostic information could be interesting targets against lung CSCs. Supported by grants RD12/0036/0025 from RTICC-FEDER, and PI12-02838 and PI15-00753 from ISCIII. Legal entity responsible for the study: Fundación de Investigación Hospital General Universitario de Valencia. Funding: Supported by grants RD12/0036/0025 from RTICC-FEDER, and PI12-02838 and PI15-00753 from ISCIII. Disclosure: All authors have declared no conflicts of interest.

Methods: A phase II randomized trial of adjuvant chemotherapy for the patients completely resected pathological stage III (T + N + M0), II, IIIA non-small cell lung cancer comparing S-1 versus S-1 with cisplatin T. Okamoto1, T. Yano2, M. Shimokawa3, S. Takeda3, K. Yamazaki1, K. Sugio4, M. Takayoyama5, A. Nagashima6, T. Tagaya7, Y. Eto8, Y. Maehara9 1Department of Surgery and Science, Kyushu University, Graduate School of Medical Sciences, Fukuoka, Japan, 2Department of Thoracic Surgery, National Hospital Organisation Beppu Medical Center, Beppu, Japan, 3Clinical Research Institute, National Kyushu Cancer Center, Fukuoka, Japan, 4Department of Thoracic Surgery and Clinical Research Institute, National Kyushu Medical Center Hospital, Fukuoka, Japan, 5Department of Thoracic and Breast Surgery, Oita University, Faculty of Medicine, Yufu, Oita, Japan, 6Department of Thoracic Oncology, National Kyushu Cancer Center, Fukuoka, Japan, 7Department of Thoracic Surgery and Clinical Research Institute, Kitakyushu Municipal Medical Center, Kitakyushu, Japan, 8Department of Surgery, Saiseikai Fukuoka General Hospital, Fukuoka, Japan

Background: Platinum-based combination chemotherapy is a standard postoperative adjuvant treatment for pathological stage II/III non-small cell lung cancer (NSCLC).

Disclosure: All authors have declared no conflicts of interest.
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Background: Randomized phase III NATCH trial in early-stage non-small cell lung cancer (NSCLC) patients (p) reported no statistically significant differences in disease-free survival (DFS) or overall survival (OS) with the addition of preoperative or adjuvant chemotherapy to surgery. In pre-operative arm, those p who achieved a complete response obtained a benefit in 5-year DFS rate (59% vs. 38%). Recently, major pathological response (MPR) to preoperative chemotherapy (10% or less of residual viable tumor after preoperative therapy) has reported as surrogate marker of OS. The aim of this study is to validate MPR as prognostic factor in a cohort of patients included in the NATCH trial.

Methods: MPR was analysed in a whole cohort of 57 early-stage NSCLC p treated in the preoperative arm into NATCH trial from 2 institutions. OS according to MPR was analysed (long-rank test) in the whole population and by histologic subtype.

Results: In this cohort, median age was 67 years (47-78), 48 p (84%) were males, 26 p (46%) squamous subtype. By stage according to 6th TNSM, 9 p (16%) stage IA, 35 p (61%) stage IB, 12 p (21%) stage IIB and 1 p (2%) stage IIA. 95% completed 3 cycles of preoperative treatment. Surgical procedures: 81 lobectomies, 14 pneumonectomies, 5 no surgery. 13 out of 57 p (22.8%) had MPR. In the whole population, there was an increase in 5-year OS among those patients with MPR compared to p without MPR (51.4% vs. 46.8%, p = 0.006). Among histologic subtypes, 5-year OS in squamous NSCLC with p with MPR was significantly longer than in p without MPR (100% vs. 48.4%, p = 0.040). Among squamous NSCLC, p with MPR had significantly shorter FFR (median 12.6 vs. 22.9 years, p = 0.010). MPR was a significant independent predictor of OS (adjusted HR aHR for DFS rate 0.75; 95% CI, 0.62-0.94, respectively; and aHR for FFR 0.27, 95% CI, 0.11-0.68, respectively).

Conclusions: MPR is a prognostic significant in squamous NSCLC p who receive preoperative chemotherapy. Validation in extended cohort merits further evaluation.

Legal entity responsible for the study: Enriqueta Felip

Disclosure: All authors have declared no conflicts of interest.

1279P

Factors predicting worse outcomes in patients with N0 lung adenocarcinoma of 3cm or smaller

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Background: The role of adjuvant chemotherapy for patients with stage I non-small cell lung cancer remains unknown. The prognostic value of histological subtypes in resected node-negative small-sized lung adenocarcinoma has not been widely investigated. This study investigated the prognostic factors in patients with node-negative lung adenocarcinoma of 3cm or smaller to find potential candidates for adjuvant chemotherapy.

Methods: A total of 746 patients with completely resected node-negative lung adenocarcinoma of 3cm or smaller were included in the study. Prognostic factors for overall survival or probability of freedom from recurrence (FFR) were investigated.

Results: The 5-year overall survival and recurrence-free rates were 86.8% and 84.8%, respectively. During follow-up, 59 (7.9%) patients developed recurrence. Univariate analysis showed that micropapillary/solid predominant group had significantly lower probability of FFR (P = 0.001) in node-negative lung adenocarcinoma of 3cm or smaller. Older age (P = 0.007), greater tumor size (P = 0.006), and micropapillary/solid predominant group (P = 0.031) had significantly lower probability of FFR in multivariate analysis.

Conclusions: The new adenocarcinoma classification has significant impact on recurrence in node-negative lung adenocarcinoma of 3cm or smaller. Patients with micropapillary/solid predominant pattern have significantly higher risk for recurrence.

Legal entity responsible for the study: None

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Disclosure: All authors have declared no conflicts of interest.

1280P

Regulatory variants in cancer-related pathway genes predict survival of patients with surgically resected non-small cell lung cancer

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Background: We conducted this study to identify genetic variants in cancer-related pathway genes which can predict prognosis of NSCLC patients after surgery, using a comprehensive list of regulatory single nucleotide polymorphisms (SNPs) prioritized by RegulomeDB.

Methods: A total of 509 potentially functional SNPs in cancer-related pathway genes selected from RegulomeDB were evaluated. These SNPs were analyzed in a discovery set (n = 354), and a replication study was performed in an independent set (n = 772). The association of the SNPs with overall survival (OS) and disease-free survival (DFS) were analyzed.

Results: In the discovery set, 76 SNPs were significantly associated with OS or DFS. Among the 76 SNPs, the association was consistently observed for 5 SNPs (ERCC1 rs2298881C > A, BRCA2 rs5092989G > A, NELL1 rs440454C > T, PPI2B RNA rs541164G > A, and LTRBP4 rs7386527G > A) in the validation set. In combined analysis, LTRBP4 rs298881C > A, BRCA2 rs5092989G > A, NELL1 rs440454C > T, and PPI2B RNA rs541164G > A were significantly associated with OS and DFS (adjusted HR aHR for OS = 1.46, 0.32, 0.76, respectively; and aHR for DFS = 1.05, 0.68, 0.75, respectively). All SNPs had significant impact on better OS (aHR = 0.75; P = 0.003).

Conclusions: Our results suggest that five SNPs in the cancer-related pathway genes may be useful for the prediction of the prognosis in patients with surgically resected NSCLC.

Legal entity responsible for the study: Jae Yong Park

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1281P

Relevance between PD-L1 and radiological invasiveness in pathological stage I lung adenocarcinoma

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Background: Programmed death ligand 1 (PD-L1) was reported to predict the response of immunotherapy; however, the association between PD-L1 expression and radiological/pathological features has yet to be elucidated.
Annals of Oncology abstracts

1282P Characterization of cancer stem cell and immune microenvironment interactions in non-small cell lung cancer (NSCLC)

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Background: Lung cancer stem cells (CSCs) are a small subpopulation of cells with self-renewal, tumorigenic properties and the ability to grow forming tumourspheres in non-adherent conditions. CSCs in non-small cell lung cancer (NSCLC) are targets poorly recognized by the immune surveillance system given that they favour an immunosuppressive microenvironment. The aim of this work was to compare the release of cytokine between monolayer cells and tumourpheres.

Methods: A total of 292 patients with resected pathological stage I adenocarcinoma were analyzed for PD-L1 expression by immunohistochemistry and evaluated to determine the association between PD-L1 expression and the radiological/pathological invasiveness. Specifically, the radiological invasiveness and non-invasiveness were determined based on the consolidation/tumor (C/T) ratio, with a cut-off value of 0.25 by thin-section computed tomography.

Results: Among 292 patients, 47 (16.1%) were positive for PD-L1 expression; the remaining 245 patients (83.9%) were negative for PD-L1 expression. Fisher’s exact test demonstrated that PD-L1 expression was significantly associated with a higher C/T ratio (P<0.029) and higher maximum standardized uptake value (SUVmax) (P=0.004).

The mean values of C/T ratio and SUVmax in patients with and without PD-L1 expression were 0.845±0.032 and 7.241±0.795, and 0.607±0.023 and 3.60±0.564, respectively (P<0.001 and P<0.001, respectively). Among 47 adenocarcinomas harboring PD-L1 expression, the frequencies of PD-L1 expression for C/T ratios of 0, 0.1–0.25, 0.26–0.5 and ≥0.51 were 6.4%, 2.1%, 4.3% and 87.2%, respectively (P<0.007).

Pathologically, PD-L1 was identified exclusively only in more invasive subtypes, not in non-invasive ones, as atypical adenomatous hyperplasia, adenocarcinoma in situ, minimally invasive adenocarcinoma, and lepidic predominant ones (P<0.001).

Conclusions: PD-L1 expression was significantly associated with radiological/pathological invasive adenocarcinomas. This study provides the first evidence of the radiological/pathological invasiveness in resected pathological stage I adenocarcinoma with PD-L1 expression.

Legal entity responsible for the study: Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1283P Non-invasive detection of lung cancer by identifying copy number aberrations in circulating cell-free DNA with next generation sequencing to aid early detection

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Background: Population stratification with molecular biomarkers could improve the cost-benefit of lung cancer screening programmes and reduce false positives. We aim to establish that somatic copy number aberrations (SCNA) are detected in circulating cell-free DNA (cfDNA) lung cancer cases. We hypothesise that the number and magnitude of SCNA might also serve as a discriminative test to aid early lung cancer detection.

Methods: Standard protocols were followed to process matched cfDNA and lymphocyte DNA for 51 untreated lung cancer cases, 30 high risk controls and 10 low-risk controls. Low coverage DNA sequencing was carried out on the Illumina HiSeq 2500 and read copy number profiles were established with the software CNAnorm. A genomic instability score was evaluated by defining the area under the receiver operating characteristic curve (AUROC).

Results: The median coverage of the genome for cfDNA was 0.49X (range 0.2X-0.63X). There was no significant difference between the median whole genome copy number aberration (CNA) score for early stage lung cancer and high risk controls, 398 (117-1353) vs 252 (149–7122) p = 0.25. The AUROC was 0.60 (95% CI 0.47-0.78) for early stage cancer (N = 21) and high risk controls compared to an AUROC of 0.74 (95% CI

Table 1282P Differences in the secretion of IL-6 and IL-8 in adherent cells and tumourspheres by multiplex analysis. Detection range of IL-6 (0.17-1750.12 pg/ml). Detection range of IL-80.28-2273.3 pg/ml

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Results: Among the 100 SNAPs tested, two SNAPs showed significant association with survival outcomes. Patients carrying the POLR2A rs2071504TT or CT genotypes showed significantly lower overall survival and disease-free survival than those carrying the POLR2A rs2071504CC genotype (HR = 1.42, 95% CI = 1.01–1.88, P = 0.01 and HR = 1.34, 95% CI = 1.01–1.67, P = 0.01, respectively). The SNP rs2288599C>T variant was found to be significantly associated with higher overall survival under the recessive model (HR = 0.13, 95% CI = 0.02–0.49, P = 0.04).

Conclusions: Our findings suggest that the POLR2A rs2071504CC>T and rs2288599C>T can influence the prognosis of early-stage NSCLC patients.

Legal entity responsible for the study: Jay Yong Park

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1286TP Neo-adjuvant chemo/immunotherapy for the treatment of resectable stage IIIA non-small cell lung cancer (NSCLC): A phase II multicenter exploratory study


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Background: Lung cancer is the primary cause of cancer mortality in western countries. The cure is unlikely in patients with NSCLC and locally advanced stage who are not surgical candidates, with a 3-year survival rate of 27% in those patients receiving chemotherapy and concomitant radiotherapy. On the contrary, in localized stages (I, II, IIIA) with surgical resection and cytostatic therapy, a survival of 5 years of 31% is achieved. Currently, there is no consensus on the best standard treatment: the surgical management of stage IIIA NSCLC remains controvertial and most patients stage IIIIB disease are generally considered inoperable. Since distant metastases remain the main site of failure, it is likely that more effective cytotoxic or other anti-tumor agents will be required. Chemotherapy stimulates an immune response against tumors, which may facilitate immunotherapy antancer activity. Evidence of synergy between chemotherapy and immunotherapy was shown in several studies.

Trial design: Phase II, single-arm, open-label multicenter study that assesses feasibility, safety and efficacy of combined neoadjuvant therapy with Nivolumab 360 mg + Paclitaxel 200mg/m2 + Carboplatin AUC6 Q3W, three cycles in resectable stage IIIA NSCLC patients followed by adjuvant treatment for 1 year with Nivolumab 240 mg Q2W for 4 months and Nivolumab 480mg Q4W for 8 months. The primary endpoint will be Progression Free Survival at 24 months from diagnosis and to assess the efficacy of the combination. The secondary endpoints will be time to progression and overall survival at 3 years, response rate, toxicity profile of the combination, the down-staging rate and complete resection rate. Also, surgical outcome and complications will be assessed. Perform correlative studies with the objectives of exploring the expression of other biomarkers, such as PD-L1, in tumor tissue, free DNA and circulating tumor cells in liquid biopsy. Describe whether PD-L1 expression is a predictive biomarker for ORR, describe PFS in PD-L1 (+ ≥1% ) population and report imaging response versus pathological response rate.

Clinical trial identification: EudraCT Number: 2016-003732-20

Legal entity responsible for the study: Spanish Lung Cancer Group

Funding: Bristol-Myers Squibb

Disclosure: All authors have declared no conflicts of interest.

1285P Association between polymorphisms in microRNA target sites and survival in early-stage non-small cell lung cancer

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Background: MicroRNAs (miRNAs) are small non-coding RNAs that function in regulation of gene expression. Recent studies have also suggested that single nucleotide polymorphisms (SNPs) located in miRNA target sites can influence the prognosis of diverse human cancers, including lung cancer. This study was conducted to evaluate the associations between single nucleotide polymorphisms (SNPs) in miRNA target sites using CLASH data and the survival outcomes of early-stage non-small cell lung cancer (NSCLC) patients.

Methods: 100 potentially functional polymorphisms were selected based on cancer-related miRNA target site in PolymiRTS database (http://comphio.uu.edu/miSNRP), CLASH data, and CancerGenes database (http://cbio.mskcc.org/cancer_genes). All polymorphisms were genotyped using SEQUENOM’s MassARRAY® iPLEX assay according to the instructions of the manufacturer. The genotype association with overall survival (OS) and disease-free survival (DFS) in 782 patients with NSCLC who underwent curative surgical resection were analyzed.

Results: Among the 100 SNPs studied, two SNPs showed significant association with survival outcomes. Patients carrying the POLR2A rs2071504TT or CT genotypes showed significantly lower overall survival and disease-free survival than those carrying the POLR2A rs2071504CC genotype (HR = 1.42, 95% CI = 1.01–1.88, P = 0.01 and HR = 1.34, 95% CI = 1.01–1.67, P = 0.01, respectively). The SNP rs2288599C>T variant was found to be significantly associated with higher overall survival under the recessive model (HR = 0.13, 95% CI = 0.02–0.49, P = 0.04).

Conclusions: Our findings suggest that the POLR2A rs2071504CC>T and rs2288599C>T can influence the prognosis of early-stage NSCLC patients.

Legal entity responsible for the study: Jae Yong Park

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Preoperative chemotherapy and radiotherapy concomitant to cetuximab in stage IIIB NSCLC: A multicenter phase II SAKK 16/01 trial

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Background: Stage IIIB NSCLC treatment is definitive chemo-radiotherapy (CRT). In our SAKK 16/01 trial, neoadjuvant chemotherapy (CT) followed by neoadjuvant accelerated radiotherapy (RT) and surgery showed a median survival of 28.7 months (mos) in selected stage IIIB patients (pts). These promising results are the rationale for the current trimodality concept, introducing concomitant cetuximab (CET) to neoadjuvant CRT.

Methods: Pts with pathologically proven resectable stage IIIB (T4N1-3M0 or T4N0M0, 6th TNM) NSCLC, PS 0-1, and adequate organ function were treated with 3 cycles of neoadjuvant CT (cisplatin 100 mg/m2 and docetaxel 85 mg/m2 d1, q3w) followed by accelerated concomitant boost RT (44 Gy in 22 fractions in 3 weeks), both with concomitant weekly CET (250 mg/m2) and subsequent surgery. The primary endpoint was progression-free survival (PFS) at 1 yr.

Results: 69 pts were treated in 11 Swiss centers. 2/3 were men, median age was 60 yrs. Histology was squamous in 41% and adenocarcinoma in 49%, with T4 disease in 61%, in 46% and both in 2%. A median relative total dose intensity of 99% of CT and 91% of CET was delivered. Per protocol RT was delivered to 95% of pts. 37 (83%) pts underwent surgery, with complete resection (R0) in 74% and a postoperative 30d mortality of 4%. Response rate after CT-immunotherapy was 57% and 64% after CRT-immunotherapy (CRT-I). Major pathologic response was found in 36% of the resected pts. 1-yr PFS based on Kaplan-Meier estimation was 50% (95% CI: 37%-62%). Median PFS was 12 mos (95% CI: 9-16), median OS was 21 mos (95% CI: 14-25), and a 2- and 3-yr survival of 41% and 36%, respectively.

Conclusions: This is one of the largest prospective phase II trials to evaluate the role of induction CRT-I and surgery in resectable stage IIIB disease, and the first to associate concurrent CET to the neoadjuvant strategy. Treatment is feasible with excellent adherence to the protocol and promising clinical and pathologic response rates, PFS and OS, supporting an aggressive approach including surgery in selected IIIB pts. As compared to our previous SAKK 16/01 experience, the addition of CET does not improve the outcome of this group of locally advanced NSCLC pts.


Legal entity responsible for the study: Swiss Group for Clinical Cancer Research (SAKK)

Funding: Merck Serono

Disclosure: All authors have declared no conflicts of interest.
Clinical trial identification: The study protocol was approved by the Institutional Review board of Shizuoka Cancer Center (28-167-28-1-3).

Legal entity responsible for the study: Haruki Kobayashi

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Abstracts

**Table: 1289PD**

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**Clinical trial identification:** The study protocol was approved by the Institutional Review board of Shizuoka Cancer Center (28-167-28-1-3).

**Legal entity responsible for the study:** Haruki Kobayashi

Funding: None

**Disclosure:** All authors have declared no conflicts of interest.

**1290P**

DNA repair gene expression in bronchial washing fluid as new molecular tool for clinical outcome decision

D. Schwenzer 1, R. Akimoto 1, J. Fardejvel, V. Sapokas 2, A. Krasauskas 2, C. Cicenas 2

1Laboratory of Molecular Oncology, National Cancer Institute, Vilnius, Lithuania, 2Department of Thoracic Surgery and Oncology, National Cancer Institute, Vilnius, Lithuania, 3Clinics of Internal Diseases, Vilnius University hospital Santariskiu Klinikos, Vilnius, Lithuania

**Background:** Platinum-based drugs (cisplatin, etc.) are used as a first-line therapy for NSCLC patients. However, such treatment is not effective for all patients. Biomarkers that could predict efficiency of the platinum-based treatment should be identified.

**Aim:** To evaluate whether the response to treatment of NSCLC patients is based on ERCC1 and RRM1 gene expression in bronchial washing fluid.

**Methods:** 70 patients with a first-time diagnosed NSCLC receiving Cisplatin+Etoposide were involved in the study. RNA was extracted from bronchial washing fluid using “RNeasy Plus Mini Kit” (QIAGEN, Germany). The analysis of ERCC1 and RRM1 expression was done by qRT-PCR method. A q2 test was used to analyze gene expression in relation to clinicopathological parameters. The survival rates were calculated by the Kaplan-Meier method. The prognostic significance was assessed by the Cox proportional hazards regression model.

**Results:** Statistically significant differences were found between ERCC1 expression and tumour differentiation grade, RRM1 expression and disease stage and lymph node status. ERCC1 expression was associated with NSCLC patient progression-free survival (PFS) rate depending on gender, disease stage, response to treatment. Patients from high ERCC1 expression group had 7.6 months longer survival than patients from low expression group. RRM1 expression was associated with NSCLC patients PFS rates depending on gender, age, tumour histology and differentiation grade. Patients from low RRM1 expression group had 7.9 months longer survival than those from high expression group. Multivariate analysis of factors influencing PFS rate showed that disease stage (p = 0.01), tumour differentiation grade (p = 0.009), response to treatment (p = 0.02) and RRM1 expression (p = 0.001) were independent prognostic factors of NSCLC patients PFS.

**Conclusions:** ERCC1 and RRM1 genes may influence platinum-based chemotherapy treatment of NSCLC patients. In order to improve the effectiveness of treatment it is appropriate to identify RRM1 expression changes in the bronchial washing fluid. Therefore, NSCLC patients with high RRM1 expression should be actively followed-up because of quicker disease progression.

Clinical trial identification: Lithuanian Bioethics Committee No. 158200-09-581-104

Legal entity responsible for the study: National Cancer Institute

Funding: None

Disclosure: All authors have declared no conflicts of interest.

**1291P**

Diagnosis and monitoring of non-small cell lung cancer patients by next generation sequencing and droplet digital PCR on circulating tumor DNA

P. Vannuffel, C. De Rop

Molecular Biology, Institut de Pathologie et de Génétique, Gosselies, Belgium

**Background:** About 80% to 85% of lung cancers are non-small cell lung cancer (NSCLC). EGFR tyrosine kinase inhibitors as well as several other targeting molecules have been demonstrated to be effective in treating patients with activating mutations. We investigated the use of circulating tumor DNA (ctDNA) and high sensitive detection techniques for mutational profiling to improve the diagnosis and monitoring of NSCLC patients.

**Methods:** ctDNA was extracted from plasma using the QIAamp Circulating Nucleic Acid Kit (Qiagen). A custom panel was designed to cover EGFR, KRAS, NRAS, BRCA, PIK3CA, IDH2, AKT1, PTEN, MET and ERBB2 hotspot mutations. Libraries, constructed according to the AmpliSeq protocol, were sequenced on the semiconductor Ion Torrent SOLiD platform. The presence of the EGFR T790M mutation was also assessed by a digital PCR assay.

**Results:** A total of 120 patients from 30 Belgian institutions were enrolled in this prospective study. The majority of patients presented with stage IV adenocarcinoma and progression. Forty-six (46) patients had a mutation detected on a former biopsy: EGFR exon 19 (26), EGFR exon 21 (8), KRAS (10), PIK3CA (1) and ERBB2 (1). Among those patients, 28 (61%) harbored the same mutation when their ctDNA was sequenced with our NGS panel: EGFR exon 19 (15), EGFR exon 21 (6), KRAS (3), PIK3CA (1) and ERBB2 (1). For 7 patients, for which no mutation had not been previously detected, 4 EGFR, 2 KRAS and 1 NRAS mutations were found after ctDNA analysis. As far as the ddPCR detection of EGFR T790M was concerned, the mutation was detected on 17 (21%) of the 34 patients presenting EGFR mutations in their prior biopsy (5 in exon 19 and 2 in exon 21). Patients with acquired T790M mutation were previously treated by Afatinib (3), Erlotinib (2) or Gefitinib (1).

**Conclusions:** Our results indicate that ctDNA can be an alternative and noninvasive source of tumor DNA, a surrogate to classical biopsies, particularly when access to tumor tissue is limited. NGS and ddPCR assays are sensitive enough to promote a clinical translation of ctDNA analysis into disease management and therapeutic decision.

Legal entity responsible for the study: Institut de Pathologie et de Génétique

Funding: Boehringer Ingelheim Institut de Pathologie et de Génétique

Disclosure: All authors have declared no conflicts of interest.

**1292P**

Safety data from randomized phase II study of cisplatin (CDDP)+S-1 versus CDDP+pemetrexed (PEM) combined with thoracic radiotherapy (TRT) for locally advanced non-squamous (non-sq) non-small cell lung cancer (NSCLC): SPECTRA study

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**Background:** Both CDDP+S-1 and CDDP+PEM could be given at full systemic doses with TRT in locally advanced NSCLC, and CDDP+PEM is one of the standard chemotherapy regimens in patients with advanced non-sq NSCLC. This multicenter, randomized, open-label, phase II study (SPECTRA) compared the efficacy and safety of the two above-mentioned promising regimens combined with TRT in patients with unresectable locally advanced non-sq NSCLC.
Methods: Patients were randomly assigned to receive CDDP ± 5-FU (CDDP 60mg/m2, d1, and 5-10mg/m2, d1-14, q2w, up to 4 cycles) or CDDP + PEM (CDDP 75mg/m2, d1, and PEM 50mg/m2, d1, q2w, up to 4 cycles) combined with TRT 60Gy in 30 fractions. The primary endpoint was 2-year progression-free survival (PFS) rate. The sample size was set at 100 patients.

Results: Between Jan 2013 and Oct 2016, 102 patients were enrolled in this study from 9 institutions in Japan. All 102 patients were eligible and assessable, of whom 52 were assigned to CDDP ± 5-FU and 50 to CDDP + PEM. Baseline characteristics were similar (CDDP ± 5-FU: PEM): median age (range) 64.5 (38.9-73.6) (32.7-74) years, women n = 17 (33%)/n = 17 (34%); stage IIIB, n = 21 (40%)/n = 20 (40%); ECOG PS of 1, n = 14 (27%)/n = 14 (28%); never smoker, n = 12 (23%)/n = 12 (24%); and adenocarcinoma, n = 47 (90%)/n = 45 (90%). Completion rate of TRT (60Gy) and chemotherapy (4 cycles) was 92% (98%) and 73% (86%), respectively. Response rate was 60%/64%. Grade 3 toxicities included febrile neutropenia (12%/2%), anorexia (8%/16%), diarrhea (8%/0%), esophagitis (6%/0%), pneumonia (4%/4%), neutropenia (3%/50%), anemia (8%/12%), thrombocytopenia (4%/6%), and hyponatremia (12%/12%). Grade 2 radiation pneumonitis was observed in 8 (15%)/2 (4%) patients. No treatment-related death was observed. The data on PFS and overall survival is immature.

Conclusions: Response rate was similar between both arms. Toxicities were tolerable and manageable in both arms; however febrile neutropenia was more frequently observed in the CDDP ± 5-FU arm. Survival data will be analyzed in late 2018.

Clinical trial identification: UMIN000009914 (release date: 31/Jan/2013)

Legal entity responsible for the study: Yuichiro Ohe

Funding: Japan Agency for Medical Research and Development

Disclosure: S. Niiho, T. Seto: Received honoraria from Taiho and Eli Lilly and research funding from Eli Lilly. K. Sakamaki, T. Yamanaka: Received honoraria from Taiho. T. Takahashi: Received research funding from Taiho and Eli Lilly and honoraria from Eli Lilly. M. Nishio, T. Hida, H. Okamoto, M. Satouchi, K. Goto, O. Yone: Received research funding and honoraria from Taiho and Eli Lilly. N. Yamamoto: Received research funding from Taiho. T. kurata: Received research funding and honoraria from Eli Lilly. All other authors have declared no conflicts of interest.

1293P

Preliminary analysis of the Spanish Lung Cancer Group (SLCG) phase II trial of concurrent chemoradiotherapy (CT-RT) with cisplatin (P) plus metronomic oral vinorelbine (mOV) for unresectable locally advanced non-small cell lung cancer (LA-NSCLC): NORA trial (GECP 15/02)


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Background: CT-RT is the standard treatment for unresectable LA-NSCLC. P plus vinorelbine is widely used. Metronomic CT is a frequent administration of low doses of non-selective drugs. M.OV has shown good efficacy and improved safety, and could improve the RT effect. Our goal is to evaluate the efficacy and safety of P-mOV with radical RT in patients (pts) with LA-NSCLC.

Methods: Pts aged 18-75 years with histologically proven untreated and unresectable LA-NSCLC, adequate bone marrow, hepatic & renal function, ECOG PS 0-1, received P 80mg/m²x D1 every 3 weeks combined with mOV 30mg/day on days D1, 3 & 5/weekly, 2 cycles (cy)/cy as induction; patients without progression received 2 more cy of P at the same dose with mOV 30mg/day on D1, 3 & 5/weekly, concurrently with RT (66Gy in 6.5weeks). Primary endpoint was progression-free survival (PFS) by RECIST v1.1; secondary endpoints were: overall response rate, overall survival and safety profile. To guarantee an overall type-I error no greater than 0.05 and a type II (β) error 0.1 for PFS, a sample size of 67 pts was planned.

Results: Since May 2016, 38 pts have been included. Fifty-three pts have been included in the analysis. P characteristics: Male 72%; median age 63 (range 33-75); PS 0/1 62/48%; smokers 48%, adenocarcinoma/squamous 43/35.9%; stage IIIA/B 35/93.9%. Non-hematological G3-4 toxicities: esophagitis 1.9%; infection without neutropenia 1.9%; dyspepsia 3.8%; thromboembolism 3.8%. No treatment-related deaths were reported.

Conclusions: mOV-P administered with RT has a manageable safety profile. Based on this, accrual is ongoing.


Legal entity responsible for the study: Spanish Lung Cancer Group (SLCG)

Funding: Spanish Lung Cancer Group (SLCG)

Disclosure: All authors have declared no conflicts of interest.
Background: Atezo (anti–PD-L1) was FDA approved for 2L NSCLC based on results from the randomized OAK and POPLAR trials, with atezo showing superior efficacy vs docetaxel (doc). We previously showed that TMB in tissue correlates with atezo efficacy in 1L docetaxel (doc). We previously showed that TMB in tissue correlates with atezo efficacy in 1L docetaxel (doc), regardless of PD-L1 expression (per VENTANA PD-L1 SP142 IHC assay). Although efficacy correlated with PD-L1 expression on tumor cells (TC) and tumor-infiltrating immune cells (IC), an OS benefit was also observed in pts with PD-L1-negative tumors (i.e., TC0 and IC0; HR, 0.75 [95% CI: 0.59, 0.96]). To determine whether these results were consistent across PD-L1 IHC assays, we assessed atezo efficacy in PD-L1 subgroups as defined by SP142 and 22C3 pharmDx PD-L1 IHC assays. 

Methods: To assess the PD-L1 IHC expression using both SP142 and 22C3 assays in the randomized OAK study, we evaluated the proportion of PD-L1–negative tumors (i.e., TC0 and IC0) as defined by both assays. We then evaluated the OS benefit in PD-L1–negative tumors with atezo vs docetaxel (doc) in OAK. These data provide evidence of atezo OS benefit in pts with PD-L1–negative tumors irrespective of the PD-L1 IHC assay used.

Results: Among the primary population of 850 pts (ITT850), 400 had results from the 22C3 assay (ITT850, 22C3), while 22C3 assay results were also available for the primary population of 850 pts with 22C3 assay results. We evaluated the proportion of PD-L1–negative tumors (i.e., TC0 and IC0) as defined by both assays. Among pts with tumors negative by SP142 and 22C3, most (77%) were also negative by 22C3 (TPS < 50%).

Conclusions: Prevalence of PD-L1 subgroups in the BEP was consistent with previous reports for both assays. Most tumors considered negative by SP142 were also negative by 22C3. An OS benefit (atezo vs doc) was observed in PD-L1–negative subgroups defined by either assay and was consistent with the overall population results from OAK. These data provide evidence of atezo OS benefit in pts with PD-L1–negative tumors irrespective of the PD-L1 IHC assay used.

Table: 12950 Clinical efficacy of atezo vs doc in bTMB subgroups

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<th>Subgroup</th>
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<tr>
<td>PFS HR (95% CI)</td>
<td>0.94 (0.72, 1.23)</td>
<td>0.90 (0.68, 1.20)</td>
</tr>
<tr>
<td>bTMB tumors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 10</td>
<td>≥ 16</td>
<td>≥ 20</td>
</tr>
<tr>
<td>No. of patients</td>
<td>96</td>
<td>63</td>
</tr>
<tr>
<td>OS HR</td>
<td>0.59</td>
<td>0.56</td>
</tr>
<tr>
<td>PFS HR</td>
<td>0.68</td>
<td>0.57</td>
</tr>
</tbody>
</table>

OAK study

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>ITT (N = 850)</th>
<th>BEP (N = 583)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS HR (95% CI)</td>
<td>0.73 (0.62, 0.87)</td>
<td>0.64 (0.53, 0.77)</td>
</tr>
<tr>
<td>PFS HR (95% CI)</td>
<td>0.95 (0.82, 1.10)</td>
<td>0.87 (0.73, 1.04)</td>
</tr>
<tr>
<td>bTMB tumors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 10</td>
<td>≥ 16</td>
<td>≥ 20</td>
</tr>
<tr>
<td>No. of patients</td>
<td>251</td>
<td>158</td>
</tr>
<tr>
<td>OS HR</td>
<td>0.69</td>
<td>0.64</td>
</tr>
<tr>
<td>PFS HR</td>
<td>0.73</td>
<td>0.65</td>
</tr>
</tbody>
</table>

BEP, biomarker-evaluable population; bTMB, tumor mutational burden in blood; ITT, intention to treat.

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Network Genomic Medicine (NGM) performs high sensitive next generation sequencing to detect co-occurring mutations and their mutual impact on overall survival. The heterogeneity of BRAF mutated lung cancer patients (pts) are poorly characterized compared to the standard therapy for V600E mutated patients. The molecular co-alterations that drive this heterogeneity of BRAF mutated lung cancer patients are the focus of this study. Aims: The aims of this study are to assess the genomic landscape and identify co-alterations driving the tumor development in BRAF V600E mutated lung cancer patients. Methods: The study is a retrospective study utilizing archival material, and the study was approved by the institutional review board. A total of 16 patients (pts) with a diagnosis of non-small cell lung cancer (NSCLC) and a confirmed diagnosis of mutated BRAF (V600E) were included in the study. Results: The genomic landscape was assessed by multigene panels using next generation sequencing followed by Sanger sequencing. The most frequent co-alteration was the mutation of PIK3CA (37.5%), followed by RB1 (37.5%), and the co-alteration of EGFR (25%). Conclusion: The results from this study suggest that PIK3CA and RB1 are the most frequently occurring co-alterations in BRAF mutated NSCLC. The co-alterations of PIK3CA and RB1 may have a significant impact on the survival of patients with BRAF mutated NSCLC. Further studies are needed to validate these findings and to determine the clinical significance of these co-alterations.
sequencing (NGS) based diagnostics on a central platform in Cologne for inoperable lung cancer pts in Germany.

Methods: The NGS panel used in NGS consists of 17 genes to cover potentially targetable alterations and is run on Illumina (MySeq) platform. In 2016, we have started the retrospective evaluation of BRAF mutated pts with available clinical data and given consent who had received NGS-based molecular diagnostics. In particular, we have focused on BRAF V600E and non-V600E mutated lung cancer pts with and without co-occurring mutations: their frequency, significance and impact on overall survival.

Results: We have analyzed 174 pts (V600E=55 pts, non-V600E=119 pts) with eligible clinical data. Co-occurring mutations were detected in 121 BRAF mutated pts (79%). The most frequent co-alteration was found in TP53 for 89 pts (74%). Regardless of treatment regimen, BRAF mutated lung cancer pts without co-occurring events seemed to have a better overall survival (OS) with 15 versus 15 months (p = 0.463), similar to the TP53 co-mutated pts (p = 0.449). Likewise, non-targeted treatment of V600E mutation seems to be a negative prognostic factor with OS 15 month versus 22 month in non-V600E mutated pts (p = 0.957).

Conclusions: We report for the first time to our knowledge the heterogeneity of BRAF mutated lung cancer pts in the largest cohort. This work provides evidence that co-occurring genomic alterations influence the overall survival of these pts and stresses the relevance of the multiplex genotyping. Further data including therapies, co-alterations in V600E and other clinicopathologic parameters will be provided.

Legal entity responsible for the study: University Hospital of Cologne for the Network Genomic Medicine

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Table: 1301PD

<table>
<thead>
<tr>
<th>OS* overall and by PD-L1 expression level</th>
<th>CheckMate 017</th>
<th>CheckMate 057</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>squamous NSCLC</td>
<td>non-squamous NSCLC</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>(95% CI)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>HR</td>
<td>HR</td>
</tr>
<tr>
<td>Overall, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-y OS rate, %</td>
<td>135</td>
<td>137</td>
</tr>
<tr>
<td>3-y OS rate, %</td>
<td>0.62 (0.48, 0.80)</td>
<td>0.74 (0.62, 0.89)</td>
</tr>
<tr>
<td>3-y OS rate, %</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>PD-L1 &lt;1% n</td>
<td>54</td>
<td>52</td>
</tr>
<tr>
<td>PD-L1 &lt;1% n</td>
<td>0.60 (0.40, 0.90)</td>
<td>0.91 (0.68, 1.21)</td>
</tr>
<tr>
<td>PD-L1 &gt;1% n</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>PD-L1 &gt;1% n</td>
<td>108</td>
<td>101</td>
</tr>
<tr>
<td>PD-L1 &gt;50% n</td>
<td>43</td>
<td>56</td>
</tr>
<tr>
<td>PD-L1 &gt;50% n</td>
<td>0.74 (0.50, 1.09)</td>
<td>0.45 (0.30, 0.63)</td>
</tr>
<tr>
<td>3-y OS rate, %</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>PD-L1 &gt;50% n</td>
<td>66</td>
<td>46</td>
</tr>
<tr>
<td>3-y OS rate, %</td>
<td>0.68 (0.27, 1.66)</td>
<td>0.35 (0.22, 0.55)</td>
</tr>
</tbody>
</table>
| Kaplan-Meier estimates CI = confidence interval; HR = hazard ratio

Results: After a minimum follow-up of 36.6 mo in each study (Feb 2017 database locks), 6% of the 427 total patients randomized to the 2 nivolumab arms remained on treatment; no patients remained on docetaxel. Nivolumab continued to show an OS benefit versus docetaxel, with 3-y OS rates of 16% versus 6% in CheckMate 017 and 18% versus 9% in CheckMate 057. Similar to prior reports, an OS benefit was observed in squamous NSCLC regardless of PD-L1 expression, and in non-squamous NSCLC was enhanced at higher PD-L1 expression levels (Table). Of 427 patients in the combined nivolumab arms, 71 (17%) had OS ≥ 3 y. Additional 3-y data across trial end-points will be presented.

Conclusions: With ≥ 3 y of follow-up from 2 randomized phase 3 studies, nivolumab continued to demonstrate an OS benefit versus docetaxel in patients with advanced squamous and non-squamous NSCLC. Overall, 3-y survival was achieved in 17% of nivolumab-treated patients.

Clinical trial identification: NCT01673867; NCT01642004

Legal entity responsible for the study: Bristol-Myers Squibb

Funding: Bristol-Myers Squibb

Disclosure: E. Felip Font: Member of advisory boards for Eli Lilly, Pfizer, Roche, Merck Sharp & Dohme, Boehringer Ingelheim. Speaker’s bureau/lecture fees from Astra Zeneca, Bristol-Myers Squibb and Novartis. S. N. Gettinger: Research funding. ARIAD, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Genentech, Incyte, Pfizer; Consulting fees: ARIAD, Bristol-Myers Squibb, Janssen. S. J. Antonia: Other from Bristol-Meyers Squibb, other from Novartis, other from Merck, other from CRBM, other from Boehringer Ingelheim, other from Genentech, other from AstraZeneca/MedImmune, other from Menegen, outside the submitted work. D. R. Spigel: Consulting/advisory roles & research funding from Genentech/Roche, Novartis, Celgene, IMS, Lilly, AstraZeneca, Pfizer, Clovis Oncology, BI research funding from Peregrine Pharma, OncoGence, OncoMed, Amgen, Verastem, Daiichi Sankyo, Merck. O. Arrieta: Personal fees from Bristol-Myers Squibb. O. A. Henley: Personal fees for advisory boards with Bristol-Myers Squibb and Roche. J. Brahmer: Advisor/consultant for BMS (uncompensated), Celgene, Eli Lilly, Merck & Co, Syndax and has received grant/trial funding from BMS, Merck & Co, MedImmune/AstraZeneca, Johnson & Johnson, Incyte, Five Prime Therapeutics. L. Q. Chow: Grants and personal fees from BMS, during the conduct of the study; grants and/or personal fees from Novartis, BMS, Merck, Eli Lilly/Imclone, Genentech, Pfizer, AstraZeneca/MedImmune, Incyte, Seattle Genetics, Sanofi Genzyme, Amgen. L. Cristin: Personal fees from advisory boards in experimental BMS, AstraZeneca, Pfizer and Merck. Participant in clinical trials sponsored by these, as well as Roche, Bi, Novartis, and Lilly. No compensation for the participation. L. Horn: Personal fees from AbbVie, Genentech, Merck, Lilly, non-financial support from Bristol-Myers Squibb, non-financial support from Xcovery, non-financial support from Bayer. W. J. Giese, A. Li: Employee of Bristol-Myers Squibb. D. Healey: Other from Bristol-Myers Squibb, during the conduct of the study; other from Bristol-Myers Squibb, outside the submitted work. E. E. Vokes: Consultant/advisory role for AbbVie, Amgen, AstraZeneca, BMS, BI, Celgene, Eli Lilly, Genentech, Lexis, Merck, Regeneron, Serono, Takeda, Ventixx. All other authors have declared no conflicts of interest.
abstracts

Annals of Oncology

1302PD

IFCT-1502 CLINIVO: Real-life experience with nivolumab in 600
patients (pts) with advanced non-small cell lung cancer (NSCLC):
Efficacy and safety of nivolumab and post-nivolumab treatment in
the French Expanded Access Program (EAP)

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Background: Nivolumab is a standard option for second-line treatment in pts with
advanced NSCLC. Real-life data are lacking regarding the efficacy of nivolumab and
post-nivolumab treatment.
Methods: This analysis included the first 600 consecutive pts with stage IIIB/IV NSCLC
who received 1 dose of nivolumab 3mg/kg q2w through the French EAP from 01/
2015 for Squamous (Sq) and 06/2015 for Non-Sq NSCLC, until 08/2015.
Results: Median age was 64 yo, there were 409 (68%) men, 521 (87%) smokers, 478
(80%) PS0/1 pts, 230 (38%) Sq and 370 (62%) Non-Sq NSCLC, 130 (22%) pts with
brain metastases. Nivolumab was administered as 2nd/3rd/4th-line for 26%/33%/41%
pts, respectively. Best response was PR/SD/PD for 17%/30%/37% of patients, respectively, with 16% not assessable. Toxicities occurred in 187 (31%) pts, including 10%
grade 3 events. After a median follow-up of 22.1 (95% CI 21.6-22.6) months, median
PFS and OS from the initiation of nivolumab were 2.1 (95%CI 1.9-2.3) and 9.5 (95%CI
8.4-10.8) months, respectively. Post-nivolumab treatment was administered to 262
(44%) pts, and mostly consisted of gemcitabine (19%), docetaxel (18%), paclitaxel
(14%), erlotinib (12%), vinorelbine (9%), platin-based doublet (8%), or pemetrexed
(8%). Access to post-nivolumab treatment was higher in PS0/1 vs. PS2 pts (48% vs.
23%, p < 0.001), but was not different according to histology or treatment line or disease control with nivolumab. Best response to post-nivolumab treatment was PR/SD/
PD for 15%/42%/42% of pts, respectively. In the whole cohort, median postnivolumab OS was 4.0 (95%CI 2.8-4.6) months, and was significantly higher in case of
PR to nivolumab (HR ¼ 0.38; 95%CI 0.23-0.64; p < 0.001), and if subsequent treatment was delivered (HR ¼ 0.30; 95%CI 0.24-2.13; p ¼ 0.001); median post-nivolumab
OS in pts receiving post-nivolumab treatment was 7.5 (95%CI 6.8-8.7) months, and
did not differ based on histology or treatment line.
Conclusions: Efficacy and safety of nivolumab was in line with available data. Postnivolumab treatment may be delivered in many pts, and impact OS. Data on the whole
cohort of 900 pts enrolled in the EAP will be presented.
Clinical trial identification: NCT02933346
Legal entity responsible for the study: French Cooperative Thoracic Intergroup
(IFCT), Paris, France
Funding: BMS
Disclosure: N. Girard: Received consultancy fees from BMS, MSD, Roche, AstraZeneca. C. Audigier Valette: Personal fees and non financial support from Roche, Lilly,
Pfizer, Boehringer Ingelheim, Astra Zeneca, Novartis, Amgen and grants from Roche,
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Honorarium from BMS. D. Moro-Sibilot: Personal fees from Roche, Eli Lilly, Pfizer,
Novartis, Astra Zeneca, BMS, MSD, Boehringer Ingelheim. O. Molinier: Personal fees
from Boehringer and served as expert for Roche, Astra-Zeneca, BMS. All other authors
have declared no conflicts of interest.

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1303PD

Nivolumab in previously treated patients with metastatic squamous
NSCLC: Results of a European single-arm, phase 2 trial (CheckMate
171) including patients aged 70 years and with poor performance
status

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D. Isla13, J. Jassem14, W. Appel15, J. Van Meerbeeck16, J. Wolf17, J. Jiang18, L.R. Molife18,
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Integrated Oncology, University Hospital of Cologne, Cologne, Germany, 18Medical
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University Hospital, Barcelona, Spain
Background: Nivolumab, a fully human PD-1 immune checkpoint inhibitor antibody,
demonstrated a favorable efficacy and safety profile in previously treated SQ NSCLC in
a phase 3 trial (CheckMate 017), with significantly longer OS (median 9.2 mo) and
fewer treatment-related (TR) grade 3–4 AEs (7%) vs. docetaxel (median OS: 6.0 mo;
grade 3–4 TRAEs: 55%). In a North American community-based study (CheckMate
153; SQ/non-SQ NSCLC), nivolumab showed comparable efficacy and safety to that
observed in controlled clinical trials.
Methods: Patients aged 18 yr from 13 European countries with advanced SQ NSCLC,
progressive disease after 1 systemic treatment, and ECOG performance status (PS) 0–
2 were eligible to receive nivolumab. The primary objective of the study
(NCT02409368) was to evaluate safety. OS and ORR were secondary objectives.
Results: 809 patients were enrolled: 79% male and 93% current/former smokers. Most
patients had received 1 (42%) or 2 (40%) prior lines of therapy. Median duration of
nivolumab therapy was 4.4 mo (range: 0.0, >14.7). 324 patients (40%) were continuing
treatment at database lock. 403 patients (50%) had TRAEs. 95 (12%) had grade 3–4
TRAEs, most frequently asthenia (12 [2%]) and fatigue (10 [1%]). Of the 5 cases (1%)
of TR grade 3–4 pneumonitis, 3 had a documented resolution, and in these patients,
resolution occurred within 5 wk. TRAEs led to treatment discontinuation in 45 patients
(6%), most commonly pneumonitis, asthenia, and fatigue (7, 5, and 5 patients each). 2
deaths were deemed TR. Median OS was 9.9 mo (95% CI: 8.7, 13.1). In the subgroup
aged 70 yr (n ¼ 279), 155 patients (56%) had TRAEs and 16 (6%) discontinued due
to TRAEs. In the subgroup with ECOG PS 2 (n ¼ 98), 45 patients (46%) had TRAEs
and 5 (5%) discontinued due to TRAEs. Additional data including outcomes in the age
70 yr and ECOG PS 2 subgroups will be presented.
Conclusions: The safety of nivolumab in this study was consistent with prior studies of
nivolumab in previously treated SQ NSCLC, with no new safety signals. Tolerability in
patients aged 70 yr or with ECOG PS 2 was comparable to the overall population.
Clinical trial identification: NCT02409368
Legal entity responsible for the study: Bristol-Myers Squibb
Funding: Bristol-Myers Squibb and Ono
Disclosure: S. Popat: Honoraria from Merck, Pfizer; served as a consultant/advisor for
BI, Eli Lilly, Novartis, Roche, Pfizer (Inst), BI (Inst), BMS (Inst), MSD (Inst); received
institutional research funding from BI, Roche, BMS, Clovis; travel: BI, MSD, BMS. A.
Ardizzoni: Honoraria from Eli Lilly, BMS, MSD, BI; served as a consultant/advisor for
Eli Lilly, BMS, MSD, BI, GSK. T. Ciuleanu: Advisor for Amgen, Astellas, AZ, BI, BMS,
Eli Lilly, Ipsen, Janssen, Merck, Novartis, Pfizer, Roche, Sandoz, Sanoi, Serono, Servier,
Teva. R. Califano: Consultant/advisor for AstraZeneca, Roche, Clovis Oncology,
Novartis, and Pfizer. R. Griffiths: Teaching honoraria from Bristol-Myers Squibb. W.
Appel: Consultant or advisor for Amgen, AstraZeneca, and Boehringer Ingelheim;
travel funding from Amgen. J. Wolf: Personal fees from University Hospital of
Cologne; grants and personal fees from AZ, Novartis, Roche, Pfizer, BI, BMS, Clovis,
and nonfinancial support from Novartis, Roche, BI, outside of the submitted work. J.
Jiang, L.R. Molife: Employed by BMS and owns stock in BMS. E. Felip Font: Honoraria
from BI, MSD, Eli Lilly, Roche, Pfizer, Novartis, BMS, Celgene; Consultant for BI,
MSD, Eli Lilly, Roche, Pfizer, Novartis, BMS, Celgene; participated on speakers’ bureau
for BMS, Novartis, and Roche. All other authors have declared no conflicts of interest.

doi:10.1093/annonc/mdx380 | 463


Background: Nivolumab (Nivo) demonstrated the promising efficacy for patients (pts) with non-small cell lung cancer (NSCLC) as second or later line treatment. And, abscopal effect of the immune checkpoint inhibitor after the radiotherapy (RT) attracts attention. However, it has not clarified the correlation of radiation pneumonitis history following RT (RPH) before Nivo and onset risk of ILD or PFS of Nivo treatments in patients with NSCLC.

Methods: 201 pts treated with Nivo from December 2015 to July 2016 were retrospectively reviewed. This study was multicenter study conducted by the three respiratory medical centers in Japan. We collected clinical data including age, sex, smoking history, histological types, performance status (PS), RT, and history of RT to chest field, at the time of starting Nivo. We evaluate the ILD and efficacy. We investigated relationship between RPH and ILD or PFS. The data cut off was on the end of November 2016.

Results: Median age was 68 years old, 135 pts were male, 157 pts had smoking history, 153 pts were PS 0 or 1, 34 pts experienced radiation pneumonitis before Nivo, and 50 pts received the RT to chest field (31 pts were curative RT). For all participants, median RPH was 2.8 months (M), overall ILD rate was 12.4%. In the incidence of ILD, no RPH vs RT: 9.6% vs 26.9% (relative risk ratio (RRR): 2.76, 95% confidence interval (CI): 1.15-4.88)). Furthermore, median PFS was no RPH vs RT: 2.3 M vs 3.6 M, non-RT to chest field vs RT to chest field: 2.2 M vs 3.3 M, and in univariate analysis, RT had a trend with higher hazard ratio (HR): 0.71, 95% CI 0.44-1.10, however RT to chest field did not correlate with PFS (HR: 1.02, 95% CI 0.69-1.47). In multivariate analysis, RT significantly correlated with PFS (HR: 0.58, 95% CI 0.35-0.93).

Conclusions: The RPH before Nivo not only gives onset risk of ILD but also contributes to the prolongation of PFS of Nivo.

Clinical trial identification: Protocol; number: UMIN000025908 release date: 31th January, 2017

Legal entity responsible for the study: Fumio Imamura

Funding: AstraZeneca. T. Kumagai: Personal fees from Ono Pharmaceutical, Astra Zeneca, Pharmaceutical. K. Nishino: Personal fees from Chyugai, Boehringer Ingelheim, Taiho Pharmaceutical, Eli Lilly Japan, Chugai Pharmaceutical, from Ono Pharmaceutical; personal fees from Pfizer, AstraZeneca, Novartis Pharma, Kyowa Hakko Kirin, Boehringer Ingelheim, Pfizer, Eli Lilly Japan, Chugai Pharmaceutical, Bristol-Myers Squibb, Merck Serono, Taisho, Kyowa Hakko Kirin, Takeda, and personal fees from Bayer. F. Imamura: Grants and personal fees from Ono Pharmaceutical, personal fees from Pfizer, AstraZeneca, Chugai, Eli Lilly, Boehringer Ingelheim, Pfizer, Merck Serono, Taisho, Kyowa Hakko Kirin, Boehringer Ingelheim, Pfizer, Eli Lilly Japan, Chugai Pharmaceutical, Bristol-Myers Squibb, S. Arai: Personal fees from Bristol-Myers Squibb, Ono Pharma, Taisho, Chugai, AstraZeneca, Eli Lilly, Boehringer Ingelheim, and grants from Ono Pharma, Pfizer, Chugai, AstraZeneca, MSD, Taisho, Yakult Pharmaceutical Industry, Eli Lilly, Boehringer Ingelheim. All other authors have declared no conflicts of interest.
Detection of driver and resistance mutations in leptomeningeal metastases of NSCLC by next-generation sequencing of cerebrospinal fluid circulating tumor cells

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Background: Leptomeningeal metastases (LM) are more common in non-small cell lung cancer (NSCLC) with EGFR mutations. The diagnosis is difficult by traditional imaging only, and leads to poor understanding of resistance mechanisms of LM.

Methods: We compared the CellSearch assayth, the Thinprep cytologic test (TCT), and brain magnetic resonance imaging (MRI) in 21 NSCLC patients with suspected LM. Next-Generation sequencing that included 416 cancer-associated genes was also performed on cerebrospinal fluid circulating tumor cells (CSFCTCs) of 19 patients.

Results: Twenty-one patients were diagnosed with LM, and CSFCTCs were captured by CellSearch in 20 patients (median, 969 CSFCTCs/7.5 mL; range, 27–14,888). CellSearch had a sensitivity of 95.2% for LM diagnosis, which was higher than that of CSFCTCs. Genetic profiles of CSFCTCs were highly concordant with molecular mutations identified in the primary tumor (17/19, 89.5%).

The resistance gene EGFR T790M was detected in 7 of 9 patients with extracranial lesions, but was only detected in 1 of 14 CSFCTCs samples. Other potential resistant mutations such as MET amplification and ERBB2 mutation were also identified in CSFCTCs.

Conclusions: CellSearch could be a more sensitive method for detecting tumor cells in CSF, and potentially provides earlier diagnosis of LM. More importantly, CSFCTCs could be an important and new way of “liquid biopsy” for genetic profiles of metastatic tumor cells in LM patients of NSCLC.

Legal entity responsible for the study: Yi-Ling Wu

Funding: Geneseq Biotechnology, Inc., Nanjing, China

Disclosure: All authors have declared no conflicts of interest.
Efficacy and safety of necitumumab and pembrolizumab combination therapy in patients with stage IV non-small cell lung cancer (NSCLC)

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Background: Studies of EGFR-directed monoclonal antibody (mAb) necitumumab (neci) and anti-PD1 pembrolizumab (pembro) demonstrate activity of each agent in NSCLC.

Methods: This phase 1b, multicenter, single arm study of neci and pembro examined the safety, efficacy, and tolerability in pretreated patients with Stage IV NSCLC (NCT02451930). PDL1 PD1 was centrally assessed retrospectively using IHC 22C3 (negative, weak positive, strong positive if < 1%, 1-4%, >50% of tumor cells were stained, respectively). Escalating doses of neci 600 – 800 mg IV (days 1 and every 4 weeks (Q4W) were administered with pembro (200 mg IV) on Day 1 Q3W (Part A). Established dose from Part A was used in the expansion cohort (Part B). Study objectives were to determine the dose-limiting toxicity (DLT) and evaluate tolerability and overall response rate (ORR) by RECIST 1.1. Secondary objectives included progression-free survival (PFS) and overall survival (OS).

Results: for 64 patients are reported. Part A completed without DLTs (9 patients; 2 squamous, 7 nonsquamous). Overall, 3 patients received neci 600 mg and 61 patients received neci 800 mg; all patients received pembro 200 mg. ORR (95% CI) was 23.4% (13.8, 35.7). Median PFS (95% CI) was 7.6 (4.2, 9.0). Six-month OS rate was 84.2% (95% CI: 76.0, 90.0).

Conclusions: The results suggest modest activity of the combination in a NSCLC patient population with a relatively high proportion of PD1L negative tumors (Table).

Table: 1309P

<table>
<thead>
<tr>
<th>Necitumumab 600 mg/800 mg + Pembrolizumab 200 mg</th>
<th>Overall (N = 64)</th>
<th>Squamous (N = 30)</th>
<th>Non-squamous (N = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), y</td>
<td>65 (43, 81)</td>
<td>67.5 (46, 81)</td>
<td>61 (43, 75)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>46 (71.3)</td>
<td>23 (76.7)</td>
<td>23 (67.6)</td>
</tr>
<tr>
<td>Prior systemic therapy, n (%)</td>
<td>1 line</td>
<td>36 (56.3)</td>
<td>22 (73.3)</td>
</tr>
<tr>
<td>2 lines</td>
<td>15 (23.4)</td>
<td>5 (16.7)</td>
<td>10 (29.4)</td>
</tr>
<tr>
<td>3 lines</td>
<td>13 (20.3)</td>
<td>3 (10.0)</td>
<td>10 (29.4)</td>
</tr>
<tr>
<td>Baseline ECOG PS, n (%)</td>
<td>0</td>
<td>64 (100)</td>
<td>30 (100)</td>
</tr>
<tr>
<td>1</td>
<td>46 (71.9)</td>
<td>26 (87.7)</td>
<td>20 (58.8)</td>
</tr>
<tr>
<td>2</td>
<td>1 (1.6)</td>
<td>1 (3.3)</td>
<td>0</td>
</tr>
<tr>
<td>Tobacco use, n (%)</td>
<td>64 (100)</td>
<td>30 (100)</td>
<td>34 (100)</td>
</tr>
<tr>
<td>Former</td>
<td>41 (64.1)</td>
<td>21 (70.0)</td>
<td>20 (58.8)</td>
</tr>
<tr>
<td>Current</td>
<td>14 (21.9)</td>
<td>7 (23.3)</td>
<td>7 (20.6)</td>
</tr>
<tr>
<td>Never</td>
<td>9 (14.1)</td>
<td>2 (6.7)</td>
<td>7 (20.6)</td>
</tr>
</tbody>
</table>

EF cacy

| ORR n (%) (95% CI) | 15 (13.3, 35.7) | 6 (20.0, 77.3) | 9 (26.5, 44.4) |
| 6-month OS rate (%) (95% CI) | 74.7 (61.5, 83.9) | 61.6 (42.8, 78.6) | 84.2 (66.0, 93.1) |

PDL1 Status

| ORR n (%) (95% CI) | 4 (3.3, 29.0) | 1 (7.7, 32.6) | 3 (11.8, 34.9) |
| 6-month OS rate (%) (95% CI) | 68.2 (47.7, 82.8) | |

PDL1 Weak positive

| ORR n (%) (95% CI) | 3 (5.0, 55.7) | 1 (4.3, 40.1) | 2 (40.0, 53.8, 5) |
| 6-month OS rate (%) (95% CI) | 93.3 (46.2, 93.6) | |

PDL1 Strong positive

| ORR n (%) (95% CI) | 4 (40.0, 72.3) | 2 (40.0, 53.8, 5) | 2 (40.0, 53.8, 5) |
| 6-month OS rate (%) (95% CI) | 76.0 (61.0, 92.3) | |

Unknown

| ORR n (%) (95% CI) | 10 (15.6) | 5 (16.7) | 5 (14.7) |
| 6-month OS rate (%) (95% CI) | 800 (40.0, 94.6) | |

Pembrolizumab 200 mg

| ORR n (%) (95% CI) | 4 (40.0, 72.3) | 2 (40.0, 53.8, 5) | 2 (40.0, 53.8, 5) |
| 6-month OS rate (%) (95% CI) | 78.8 (38.1, 94.9) | |
Background: Atezolizumab (atezo; anti–PD-L1) inhibits binding of PD-L1 to PD-1. A phase III study of atezo vs docetaxel (doc) in 2L/3L NSCLC demonstrated a superior OS benefit of atezo (HR 0.73; 95% CI 0.62, 0.87; P = 0.0003) in patients regardless of PD-L1 expression levels on tumor cells (TC) or tumor-infiltrating immune cells (IC). Here we present efficacy and safety analyses in the OAK primary population (n = 850) by BOR subgroups.

Methods: Previously treated pts were randomized 1:1 to atezo (1200 mg) or doc (75 mg/m2) IV q3w. Co-primary endpoints were OS in ITT and PD-L1 expression subgroups.

Results: Baseline demographics were generally similar across BOR subgroups except for CR/PR which was observed across BOR subgroups with greatest benefit occurring in the CR/PR subgroup (HR 0.32; 95% CI 0.16, 0.63; see Table). Among pts in the CR/PR subgroup, the median time to event was 13.8 mo (11.8, 15.7) in patients with BOR as CR/PR. No new safety findings were observed among BOR subgroups.

Conclusions: Atezo responses were durable. Atezo responders had more than two-thirds reduction in the risk of death compared with doc responders. In agreement with the improved OS with atezo vs doc seen in pts with SD and PD suggests that clinical benefit also extended to patients who did not have a radiographic response.

Table 1310P Efficiency of atezolizumab vs docetaxel by BOR subgroups

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Atezolizumab</th>
<th>Docetaxel</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT (N = 850)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mOS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mOS, (95% CI), mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR/PR</td>
<td>425</td>
<td>9.6 (8.6, 11.2)</td>
<td>0.73 (0.62, 0.87)</td>
</tr>
<tr>
<td>SD</td>
<td>150</td>
<td>17.6 (15.7, 20.2)</td>
<td>0.70 (0.53, 0.92)</td>
</tr>
<tr>
<td>PD</td>
<td>187</td>
<td>7.3 (6.7, 9.4)</td>
<td>0.72 (0.56, 0.93)</td>
</tr>
<tr>
<td>Stratified HR for ITT and unstratified HR for subgroups: 95% CI for HR were estimated using Cox regression.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NE, not estimable.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical trial identification: NCT02008227

Legal entity responsible for the study: F. Hoffmann - La Roche Ltd.

Funding: F. Hoffmann - La Roche Ltd.

Disclosure: F. de Marinis: Consultation fees received from Roche/BMS/Boehringer/Novartis/Pfizer/MSD/AstraZeneca. F. Barlesi: Honorarium from Roche. A. Rittmeyer: Grants as an advisor or speaker by: Astra Zeneca, BMS, Boehringer Ingelheim, Eli Lilly, Pfizer and Roche Genentech. J. von Pawel: Board: ABBV; Pfizer, Bristol Myers Squibb, Novartis money paid to the institution. A. Spiria: Research sponsored by Roche/Genentech (payable to institution), Speakers bureau. D. B. Gandara: Consultant: Genentech Clinical trial grant: Genentech. W. Yu: Genentech Employee. P. He: Employee of Roche/Genentech, and have stocks for Roche, Amgen. J. von Pawel has stock in Roche, Amgen. Husbands have stock for Allergan and Gilead. C. Yun: Employee of Genentech, Roche stock, Research funding from Genentech M. Ballinger: Employee of Genentech, Roche stock. M. Gandhi: Employee of Genentech. S. Gadgell: Speaker’s bureau: Astra-Zeneca, Genentech/ Roche Advisory Board- Astra-Zeneca, Ariad, Pfizer, Bristol Myers Squibb and Genentech/Roche. All other authors have declared no conflicts of interest.

1311P LKB1 loss is a novel genomic predictor of de novo resistance to PD-1/PD-L1 blockade in KRAS-mutant lung adenocarcinoma

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Background: Previously reported that KRAS-mutant lung adenocarcinomas (LUAC) with co-occurring genetic events in STK11/LKB1 or TP53 (KP) define subgroups with marked differences in immune contexture, including paucity of infiltrating CD8+ lymphocytes in KL LUACs. Here, we present updated data on the clinical efficacy of PD-1/PD-L1 inhibitors in lung cancer subgroups defined based on RECIST v1.1 response determined by investigators. Time to response (TTR) was based on tumor assessment every 6 weeks. Data cut-off, July 7, 2016.

Methods: Patients (pts) with metastatic KRAS-mutant LUAC who received at least one cycle of PD-1/PD-L1 inhibitor therapy, were alive for at least 14 days thereafter, and had available molecular profiling were identified retrospectively. Efficacy assessment was based on RECIST v1.1. PD-L1 expression was tested using 22C3 pharmDx or E1L3N IHC assays. Isogenic derivatives of the LKR10-KRAS+/LKB1+ murine LUAC cell line with CRISPR/Cas9-mediated LKB1 knockout were used in preclinical experiments.

Results: 192 immunotherapy-treated (82% nivolumab, 5% anti-PD-1/PD-L1 plus CTLA-4) pts with KRAS-mutant LUAC were included in the analysis. The ORR differed significantly between the KR (8.9%), KP (37.9%) and K-only subgroups (28.9%) (P = 0.00069, Fisher’s exact test) and was concordant for each genotype across patient cohorts (ORR for KR 8.3% in the MDA cohort, 8.7% in the MSKCC cohort and 9.5% in the DFCI/MGH cohort). KL LUAC exhibited significantly shorter PFS (mPFS 1.8m vs 3m, HR 0.40, 95% CI 0.22, 0.75, P = 0.0012, log-rank test) compared to KRAS-mutant LUAC with wild-type LKB1. 11/14 KL tumors with available IHC data were negative for PD-L1 expression. Among 7 PD-L1-negative KP tumors, 3 PRs and 2SDs were recorded. In syngeneic murine models loss of LKB1 promoted resistance to PD-1 inhibitor monotherapy, suggesting a causative role. Conclusions: Inactivation of LKB1 represents a novel genomic predictor of de novo resistance to PD-1/PD-L1 blockade in KRAS-mutant LUAC. In addition to tumor PD-L1 status and tumor mutational burden precision immunotherapy approaches should take into consideration the LKB1 status of individual tumors.

Legal entity responsible for the study: the phase III NSCLC OAK study


Disclosure: F. Hoffmann - La Roche Ltd. - (Other)

Legal entity responsible for the study: F. Hoffmann - La Roche Ltd.

Funding: F. Hoffmann - La Roche Ltd.

including 1 platinum-based (ATLANTIC). Per exploratory analysis, the first 2 post-baseline assessments were used to develop the model. Using an elastic net statistical method, a single variable (interpretable as a weighted average), and identified the optimal score thresholds to segment pts into 2 groups (‘good’ vs. ‘bad’) with significant differences in long-term OS.

Results: As of June 3, 2016, 444 pts had received treatment; 191 from cohort 2 (EGFR/ALK wild-type pts) with sufficient assessments (baseline and ≥ 1 follow-up) were used to develop the model. Median age was 64.0 years, 61.8% had WHO PS 1, 18.8% had squamous histology, mean number of prior anticancer regimens was 4.6, and 83.7% were current/ex-smokers. PD-L1 expression was high (≥25% of tumor cells stained) in 57.1%, low/negative in 35.6%, and unknown in 7.3%. OS results are summarized in the table. The model was validated using data from a Phase I/II open-label trial of durvalumab (1108).

Conclusions: We developed an algorithm based on baseline characteristics and tumor assessments to segment NSCLC pts treated with durvalumab into 2 groups with distinct OS. The scoring system was independently validated. However, the predictive versus prognostic value of this algorithm needs further evaluation using data from randomized trials.

Clinical trial identification: NCT02087423 (release date: March 4, 2014)

Legal entity responsible for the study: AstraZeneca PLC

Funding: AstraZeneca


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Table: 1312P

<table>
<thead>
<tr>
<th></th>
<th>ATLANTIC (model building)</th>
<th>Study 1108 (validation)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bad Group (n = 157)</td>
<td>Good Group (n = 34)</td>
</tr>
<tr>
<td>Median OS (95% CI), days</td>
<td>340 (292, 403)</td>
<td>NE (557, NE)</td>
</tr>
<tr>
<td>6-month OS rate (95% CI)</td>
<td>0.742 (0.665, 0.804)</td>
<td>0.941 (0.785, 0.985)</td>
</tr>
<tr>
<td>1-year OS rate (95% CI)</td>
<td>0.478 (0.397, 0.554)</td>
<td>0.882 (0.716, 0.954)</td>
</tr>
<tr>
<td>HR (Good vs. Bad) (95% CI)</td>
<td>0.2059 (0.0569, 0.4437)</td>
<td>0.2637 (0.1661, 0.4187)</td>
</tr>
</tbody>
</table>

NE, not estimable

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Background: A superior survival benefit with atezolizumab (atezo, anti-PD-L1) vs docetaxel (doc; HR 0.73; 95% CI 0.62, 0.87) has been demonstrated in OAK, the first randomized Phase III study of atezo in NSCLC patients (pts) who had failed prior platinum therapy. In the primary efficacy population (n = 850), atezo benefit was seen regardless of PD-L1 expression levels on tumor cells (TC) or tumor-infiltrating immune cells (IC). Here, we present the analyses of irAEs in the safety population (N = 1225) of OAK.

Methods: Pts were randomized 1:1 to atezo (1200 mg) or doc (75 mg/m²) IV qw. Co-primary endpoints were OS in ITT and in PD-L1 expression subgroups. Secondary endpoints included ORR and safety. irAEs were defined using MedDRA Preferred Terms that included both diagnosed immune conditions and signs and symptoms potentially representative of immune related events, regardless of investigator-assessed causality. Safety analyses conducted were incidence, nature and severity of irAEs, corticosteroid use and irAEs leading to atezo interruption/discontinuation. Data cutoff: July 7, 2016.

Results: In the atezo arm, 6.2% of pts had grade 3-4 irAEs and 25.0% of pts had grade 1-2 irAEs. No grade 5 irAEs were reported. Low rates of any-grade hypothyroidism (3.9%), pneumonitis (1.5%), hepatitis (1.1%), and colitis (0.3%) were observed. Grade 3-4 irAEs included pneumonitis (0.7%) and hepatitis (0.7%); no pts developed Grade 3-4 colitis. 36 (5.9%) atezo arm pts experienced irAEs requiring corticosteroid treatment. Majority of irAEs in the atezo arm were manageable; 13 pts (2.1%) discontinued atezo. Meningoencephalitis (0.7%) and AST/ALT elevation (0.9%/0.2%) were the most frequently reported irAEs leading to atezo discontinuation. 26 pts (4.3%) had dose interruptions due to irAEs. AST/ALT elevation (0.8%/0.6%) and diarrhea (0.8%) were the most frequently reported irAEs leading to dose interruption.

Conclusions: The irAEs occurring in atezo-treated pts were mostly low grade and manageable, with few pts requiring dose interruption/discontinuation of atezo and corticosteroid treatment. Efficacy data based on irAE subgroups of OAK are presented separately.

Clinical trial identification: NCT02008227

Legal entity responsible for the study: F. Hoffmann - La Roche Ltd.

Funding: F. Hoffmann - La Roche Ltd.


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Immune-related adverse events (irAEs) in advanced NSCLC patients treated with atezolizumab: Safety population analyses from the Ph III study OAK


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1313P
In this analysis, irAEs did not negatively impact the survival benefit of corticosteroids. Median OS in pts who did vs did not receive corticosteroids was 16.0 mo (95% CI: 11.7, 21.2). 24 atezo arm pts (6%) required corticosteroid treatment. A TD Cox model was in favor of atezo arm pts with irAEs vs those without irAEs (HR 0.73; 95% CI: 0.62, 0.87).

Results:

The incidence of irAEs in the atezo arm was 31% (25.0% grade 1-2, 6.2% grade 3-4, no grade 5). Baseline characteristics including PD-L1 expression on tumor cells or tumor-infiltrating immune cells were generally similar between irAE subgroups. OS per TD Cox model was in favor of atezo arm pts with irAEs vs those without irAEs (HR 0.79; 95% CI: 0.60, 1.05). Median time to onset of first irAE was 1.6 mo; post irAE mOS was 17.3 mo (95% CI: 11.7, 21.2). 24 atezo arm pts (6%) required corticosteroid treatment. Median OS in pts who did vs did not receive corticosteroids for irAEs (HR 0.90; 95% CI: 0.73, 1.24; n = 25) vs 21.9 mo (95% CI: 16.6, 14.3; n = 12), respectively. Median FFS was 5.9 mo (95% CI: 5.2, 6.4) vs 3.4 mo (95% CI: 4.2, 8.8) and ORR was 29% (95% CI: 13, 51) vs 21% (95% CI: 13, 36) in pts who did vs did not receive corticosteroids.

Conclusions: In this analysis, irAEs did not negatively impact the survival benefit of atezo. Further investigation on the impact of corticosteroids on atezo efficacy in randomized trials is needed.

Clinical trial identification: NCT02008227

Legal entity responsible for the study: F. Hoffmann - La Roche Ltd.

Funding: F. Hoffmann - La Roche Ltd.

interim data on response rates, survival and safety as well as baseline QoL, and its changes are presented.

Methods: Adult pts with advanced refractory NSCLC received Nivo 3 mg/kg q2w. Tumor response was assessed using RECIST v 1.1, adverse events (AEs) with NCI CTCAE v3.0; for QOL and symptom assessment RAND SF-36 and EASAS-R were used. Progression-free survival (PFS) and overall survival (OS) from the start of Nivo treatment were evaluated using Kaplan-Meier method. Group Qol comparisons were made using Mann-Whitney and Wilcoxon tests.

Table: 1316P Preliminary response data stratified for PD-L1 (Study in progress)

<table>
<thead>
<tr>
<th>NSCLC (n = 26)</th>
<th>PD-L1 (22C3 IHC) (n = 20)</th>
<th>IHC not available n = 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1 expression</td>
<td>PR, n (%)</td>
<td>SD, n (%)</td>
</tr>
<tr>
<td>&lt;1%</td>
<td>3 (27%)</td>
<td>7 (64%)</td>
</tr>
<tr>
<td>1-49%</td>
<td>2 (50%)</td>
<td>4 (25%)</td>
</tr>
<tr>
<td>≥50%</td>
<td>4 (80%)</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>1 (17%)</td>
<td></td>
</tr>
<tr>
<td>SD, n (%)</td>
<td>3 (50%)</td>
<td></td>
</tr>
</tbody>
</table>

AM0010 plus anti-PD1 increased Th1 and Th2 cytokines and FasL in the serum and led to a sustained increase in the number and proliferation of PD1+ Lag3+ activated CD8+ T cells, suggesting the invigoration of previously exhausted CD8+ T cells. In addition, previously undetectable T cell clones in the blood expanded to rank amongst the most abundant clones in the patient. The magnitude of novel T cell expansion and the number of invigorated CD8+ T cell correlated with objective tumor responses.

Conclusions: AM0010 in combination with anti-PD-1 is well-tolerated in advanced NSCLC pts. AM0010 improved on the expected response rates of nivolumab regardless of PD-L1 status. The observed CD8+ T cell activation is promising and encourages the continued study of AM0010 in combination with an anti-PD-1.

Clinical trial identification: NCT02099449

Legal entity responsible for the study: ARMOR Biosciences, Redwood City, CA, USA

Funding: ARMOR BioSciences, Redwood City, CA, USA

Disclosures: P. V. Vlassaeva: Employment, Stock, board of directors, A. Hung: Employment, G. Brown, M. Oft: Employment. All other authors have declared no conflicts of interest.

Multicenter observational study of the efficacy and safety of nivolumab (Nivo) as 2+ line treatment and quality of life (QoL) in advanced refractory non-small cell lung cancer (NSCLC) interim analysis


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Background: We aimed to evaluate clinical and patient-reported outcomes of Nivo as ≥ 2nd line treatment in NSCLC pts within the expanded access program. The
1319P Efficiency of nivolumab in the treatment of second-line advanced non-squamous non-small cell lung cancer (NSCLC) in Spain

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Background: The aim was to estimate the cost per life year gained (LYG) and quality-adjusted life year (QALY) of nivolumab compared to the standard of care, docetaxel, as second-line (2L) treatment in advanced non-squamous (NSQ) NSCLC patients in Spain.

Methods: An economic model with 3 health-states: progression free (PF), progressive disease (PD) and death was used to simulate, for a lifetime horizon, the total costs and outcomes for both therapies. Dosages for both therapies were derived from Summary Characteristics. Costs and outcomes were discounted (3% annually). Sensitivity analyses (SA) were performed to verify the model robustness.

Results: Nivolumab was more effective than docetaxel, yielding 0.96 LYG and 0.81 additional QALY per patient. Total cost was higher with nivolumab (increment of €31,656), mainly driven by 2L drug and follow-up cost. Incremental ratios were €41,431/LYG and €45,738/QALY at public list prices (confidential reimbursed price was used in an alternative analysis), administration, grade 3-4 AE management, monitoring, and follow-up disease management at PF, PD and “end of life” care. Dosages for both therapies were derived from Summary Characteristics. Costs and outcomes were discounted (3% annually). Unitary costs were obtained from a national costs database. Resources consumption for AE, disease management and pattern for 3L were defined by local oncologists. Sensitivity analyses (SA) were performed to verify the model robustness.

Conclusions: Considering a willingness-to-pay threshold of €30,000–€45,000/QALY gained, nivolumab versus docetaxel could be considered a cost-effective option for 2L treatment in Spanish patients with NSQ NSCLC.

Legal entity responsible for the study: Bristol-Myers Squibb

Disclosure: P. González, C. Garriño: Employee of BMS. N. Ortega-Isaqui: Employee of PORIB (consultant company) has received financial support from BMS regarding the development of the present project. C. Garriño: Financial support from BMS regarding the development of the present project. M. Echave: Employee of PORIB (consultant company) has received financial support from BMS regarding the development of the present project.
Baseline corticosteroids (CS) could be associated with absence of benefit to immune checkpoint inhibitors (ICI) in advanced non-small cell lung cancer (NSCLC) patients

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Background: Concomitant use of corticosteroids (CS) during immune checkpoint inhibitors (ICI) therapy are not recommended, but their real impact on ICI efficacy remains unknown. The aim of this study was to assess the impact of CS on ICI outcomes in NSCLC patients.

Methods: Baseline CS intake and dose, patient characteristics and outcome were retrospectively collected in patients treated with PD1/PDL1 inhibitors from Nov. 2012 to Mar. 2017 in our Institute. Primary endpoints were overall survival (OS) and disease control rate (DCR; complete response + partial response + stable disease) and secondary endpoint was progression free survival (PFS).

Results: We enrolled 244 pts. Median age was 63 years (30-85), 158 (65%) were males, 212 (87%) smokers, 196 (80%) PS 0-1, 155 (64%) had non-squamous cells carcinoma. Median of prior line of therapy was 3 (0-11). KRASmut and EGFRmut were present in 62 (25%) and 14 (6%) of NSCLC, 3 (1%) were ALK+, 64 (26%) PD-L1+ (cut-off 1% of tumor cells), 24 (10%) PD-L1- and 156 (64%) PD-L1 unknown. In the whole population, the overall response rate (ORR) was 29% and DCR 50%. Median OS and PFS were 9 months (m) [6-12] and 2m [2-3], respectively. The median follow-up was 10m [7-12]. Sixty-six patients (27%) received CS at baseline. Main reasons for taking CS were dyspnea (49%) and brain metastasis (15%). The median dose of daily prednisone was 16.25 mg [5;32.75] and >20mg in 19 (29%). CS dose >20mg was an independent factor for poor OS (HR 1.013, 95% CI 1.006; 1.02, p < 0.011). For patients taking CS >20mg, the median OS was 3m [2-12] vs. 10m [7-15] for <20mg (p = 0.005). The median PFS for >20mg was 1m [1-4] vs. 3m [2-4] for <20mg (p = 0.002). CS >20mg was also significantly associated with progressive disease (p = 0.011).

Conclusions: Baseline daily prednisone intake of at least 20mg is associated with poor outcomes in advanced NSCLC treated with ICI. Further prospective studies are awaited for validating the real impact of CS in ICI efficacy.

Legal entity responsible for the study: Dr Benjamin Besse

Funding: Institut Gustave Roussy

Disclosure: D. Planchard: AstraZeneca Boehringer Ingelheim BMS Lilly MSD Pfizer Roche Novartis Chugai. J-C. Soria: AstraZeneca, Astex, Clovis, GSK, Gumamabbs, Lilly, MSD, Mission Therapeutics, Merus, Pfizer, Pharmamar Pierre Fabre, Roche-Gemtech, Sanofi, Servier, Symphogen, Takeda. All other authors have declared no conflicts of interest.

Generalization and representativeness of phase III immune checkpoint inhibitor trials in NSCLC

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Background: Immune checkpoint inhibitors (ICBs) have become standard treatment in platinum-failed non-small cell lung cancer (NSCLC) based on several phase III studies. Recent randomized phase III trials have led to the approval of ICB. However, strict criteria for patient enrollment of phase III trials raise questions regarding generalization in the real world. The aim of this study was to evaluate whether pivotal phase III trials using ICB represent the real world NSCLC patients.

Methods: We reviewed the inclusion/exclusion criteria of 3 practice changing phase III trials (CheckMate057, CheckMate017, KEYNOTE-010). Availability of tumor tissue and other exclusion criteria for KEYNOTE-010 were additionally checked. We retrospectively analyzed the database of stage IIIB or IV NSCLC patients diagnosed from 2011 to 2013 at Seoul National University Hospital (cohort 1). We also analyzed the criteria in 53 NSCLC patients who have treated with nivolumab or pembrolizumab as a routine practice (cohort 2).

Results: Among the 715 NSCLC patients in cohort 1, 499 (69.9%) were ineligible for 3 trials. Reasons for ineligibility were as follows: no platinum doublet 23.6%, lack of tissue 22.7%, the Eastern Cooperative Oncology Group performance status ≥ 1 14.1%, steatosis 18.2%, active central nervous system metastasis 8.3%, hepatitis B or C virus human immunodeficiency virus 8.9% and no measurable lesion 7.3%. EGFR mutation was more common in ineligible group than eligible group (44.7% vs 19.7%, P < 0.001) in cohort 2 which comprise 53 patients who received ICB as a routine practice, 67.9% were classified as ineligible group. Treatment outcomes of ICB in cohort 2 seems to be inferior than those of 3 trials: response rate of 11.3%, disease control rate of 26.4%, and median progression-free survival of 1.67 months.
**Background:** A long-term follow-up on an earlier published clinical trial of 15 stage III-IV NSCLC patients treated with and IDO peptide vaccine.

**Methods:** 15 patients with stage III-IV NSCLC in disease stabilization after standard chemotherapy were treated with subcutaneous vaccinations (100 µg IDO3 peptide, seq 
20, 221–232 ALLEIASCL, in 400 µL Montanide). Patients were enrolled from 2010 to 2012 and treated biweekly for 2.5 months and thereafter monthly up to progression or up to 5 years. As published in Clin Cancer Res 2013, the vaccine was well tolerated and a long-lasting PR + SD (>8.5 months) was seen in 47% of the patients. A long-term follow-up has been made, investigating the long term clinical benefit and immunity.

**Results:** 3 of the 15 patients are still alive (May 2017) corresponding to a 5-year overall survival of 20%. One was excluded due to progression after 11 months; the other two lasting PR

**Conclusions:** The vaccine has been well tolerated for all 5 years. Analyses of PBMCs every 3rd to 6th month during treatment showed that the patient had no sign of malignancy and has been tumour free ever since. The vaccine is therefore a promising approach to the treatment of metastatic lung cancer patients vaccinated with an epitope derived from indoleamine 2,3 dioxygenase (IDO) in a phase I study.

**Legal entity responsible for the study:** J.K. Keldsen 1, T.Z. Iversen 2, L.E. Noerregaard 3, A. Mellinggaard 4, M.H. Andersen 1, M.A. Swane 5

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**Disclosure:** All authors have declared no conflicts of interest.
Systematic inflammation and histologic grade in non-small cell lung carcinoma

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Background: Tumor grade is an important factor of cancer outcome. Systematic inflammation has been associated with tumorigenesis and tumor aggressiveness and prognosis in several human malignancies. Cancer cells create an inflammatory peritumoral microenvironment by releasing a number of cytokines.

Methods: In total, 108 patients (88 males) with histologically proven NSCLC and no signs of active infection were evaluated. Tumor grade was examined and systematic inflammatory response was assessed by circulating levels of C-reactive protein (CRP), albumin, ferritin, transferring and the modified Glasgow Prognostic Score (mGPS). Patients were followed up and survival data were subsequently collected. Associations with medical, pathological, histological parameters and patients’ survival were studied.

Results: Histological grade was associated with tumor size, the presence of pathological lymph nodes, organ metastases and advanced disease stage (p < 0.010, p < 0.001 and p < 0.001, respectively). There was a trend of higher histological grade in adenocarcinomas compared to squamous carcinomas (p = 0.263). High histological grade was also significantly associated with elevated serum CRP levels (p < 0.001), hypoalbuminemia (p = 0.009), elevated ferritin levels (p = 0.049), abnormal mGPS (p = 0.048) and a trend for reduced transferrin levels (p = 0.101). In multivariate analysis, histological grade, stage, ECOG performance status and mGPS were identified as independent prognostic factors for overall survival (Cox regression analysis, p < 0.002, p < 0.001, p = 0.010 and p = 0.019, respectively).

Conclusions: Our data support the association of tumour grade with the presence of systemic inflammation; two well described negative prognostic factors for NSCLC. To our knowledge this is the first time that these factors are associated with each other giving more information about the prognosis in patients with NSCLC.

Legal entity responsible for the study: None

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Impact of next generation TKI and co-occurring mutations in ALK-positive NSCLC patients: Results of the Network Genomic Medicine

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Background: While the first NGEV in 2013 already showed a survival benefit of pts with activating genetic aberrations in EGFR and ALK, our current evaluation shows the heterogeneity of ALK-positive lung cancer pts and, for the first time to our knowledge, the impact of co-occurring mutations in these pts cohort. This work provides evidence for the efficacy of sequential ALK inhibitor treatment using next generation inhibitors and underlines the relevance of multiplex genotyping. Legal entity responsible for the study: University Hospital of Cologne for the Network Genomic Medicine

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Detection of EGFR T790M in Asia-Pacific patients (pts) with EGFR mutation-positive advanced non-small cell lung cancer (NSCLC): Circulating tumour (ct) DNA analysis across 3 platforms

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Background: Osimertinib is an oral, potent, CNS active, irreversible EGFR-TKI approved to treat pts with T790M-positive NSCLC. Non-invasive methods to confirm presence of T790M are needed to identify pts who might benefit.

Methods: AURA17 (NCT02442349) is a Phase II, single arm study investigating the safety and efficacy of osimertinib 80 mg once daily in an Asian-Pacific pt population with T790M positive advanced NSCLC, who had disease progression following EGFR-TKI therapy. Tumour tissue T790M status was centrally confirmed by cobas® EGFR Mutation Test (Roche Molecular Systems). Where possible, matched plasma ctDNA samples collected at screening were analysed for EGFR mutations using 3 tests: cobas® EGFR Mutation Test and Multiplex genotyping using SuperARMS, and droplet digital PCR (ddPCR, in-house research assay).

Results: Table summaries concordance data.

Table: 1331P Sensitivity and specificity of plasma tests using ctDNA test as the reference

<table>
<thead>
<tr>
<th>% (95% CI)</th>
<th>cobas plasma</th>
<th>SuperARMS</th>
<th>ddPCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 240)</td>
<td>(n = 249)</td>
<td>(n = 249)</td>
<td></td>
</tr>
<tr>
<td>T790M</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPA</td>
<td>42 (34, 50)</td>
<td>49 (41, 57)</td>
<td>56 (48, 64)</td>
</tr>
<tr>
<td>NPA</td>
<td>83 (72, 91)</td>
<td>78 (67, 86)</td>
<td>73 (62, 81)</td>
</tr>
<tr>
<td>LB58R</td>
<td>65 (54, 75)</td>
<td>NA*</td>
<td>62 (51, 72)</td>
</tr>
<tr>
<td>NPA</td>
<td>100 (98, 100)</td>
<td>NA*</td>
<td>99 (96, 100)</td>
</tr>
<tr>
<td>Exon 19 deletions</td>
<td>86 (80, 92)</td>
<td>NA*</td>
<td>66 (58, 74)</td>
</tr>
<tr>
<td>NPA</td>
<td>97 (91, 99)</td>
<td>NA*</td>
<td>98 (93, 100)</td>
</tr>
</tbody>
</table>

NPA, negative percent agreement (specificity), PPA, positive percent agreement (sensitivity), *SuperARMS used solely for detection of T790M Number of patients tested with cobas tissue test: 277 In the evaluable for response (EFRR 4 March 2016 data cut-off) set, pts with T790M-positive status by both tumour and plasma analysis had confirmed objective response rates (ORR with osimertinib (RECIST 1.1 by blinded independent central review) of 56% (95% CI 43, 69, 36/64 pts) using cobas plasma, 64% (52, 74, 49/77 pts) using SuperARMS, and 56% (45, 67, 49/87 pts) using ddPCR. ORR in the overall EFRR tumour T790M-positive population was 60% (52, 68, 100/166 pts).

Conclusions: Using cobas tissue test as the reference, sensitivity for plasma T790M detection slightly increased with superARMS and ddPCR compared to cobas plasma test. Conversely, specificity slightly decreased. In pts with tumour T790M positive status ORR with osimertinib was consistent across plasma tests, and with the overall tumour T790M-positive population. Biopsy is recommended for pts with a plasma T790M-negative test result, where feasible.

Clinical trial identification: NCT02442349

Legal entity responsible for the study: AstraZeneca

Funding: AstraZeneca

Annals of Oncology
Influence of plasma T790M mutation on clinical decision after 1st generation EGFR-TKI resistance in a real-world study

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Background: T790M mutation detection in circulating tumor DNA (ctDNA) has shown great potential in clinical application. However, few studies reported the influence of plasma T790M mutation on selection of clinical treatment and survival time after first generation TKI resistance.

Methods: 307 patients with advanced or recurrent NSCLC who had progressed during EGFR-TKIs treatment were enrolled prospectively (NCT02418234) from March 2015 to March 2016. Blood samples were drawn within two weeks from PD occurred. T790M mutations were evaluated by droplet digital PCR. We undertook follow-up every 3 months by phone till April 2017. The median follow-up time was 11 months (range, 2 to 22 months).

Results: Our results showed that the median survival time after TKI progression was 17.5 months (95% CI 15–20 months) and six kinds of treatments were used in these patients, including continuation of TKI (27.0%), AZD9291 (27.6%), chemotherapy, or without radiotherapy (15.3%). TKI combined with chemo/RT (6.5%), switch to another TKI (2.6%), and best supportive care (11.4%). 88.6% of patients received subsequent treatment. T790M+ patients were likely to receive continuation of original TKIs, which accounts for 29.5% (52/176), the percentage of switch to another TKI is the lowest (2.8%, 5/176). In T790M+ patients, AZD9291 is the first choice as the subsequent treatment, which accounts for 38.9% (51/131). Switch to another TKI (2.2%, 3/131) and TKI combined with chemo/RT (6.1%, 8/131) is the least selection. Although most T790M+ patients received continuation of original TKIs, combination of TKI and chemotherapy/radiation therapy seems to be a better choice, which got the longest survival than other treatment. For T790M+ patients, patients who choose AZD9291 had the longest survival.

Conclusions: T790M status in ctDNA have the great influence on clinical decision of the subsequent treatment. AZD9291 is the most frequent choice for the plasma T790M+ patients, which contributed the longest survival after 1st generation EGFR-TKI resistance.

Clinical trial identification: NCT02418234

Legal entity responsible for the study: Shenglin Ma

Funding: Projects of Medical and Health Technology in Zhejiang Province (WKJ-2J-1532)

Disclosure: All authors have declared no conflicts of interest.
Background: To date, the frequency of EGFR T790M in TKI-naïve patients remains unclear, ranging from 2% to 80% depending on the sensitivity and specificity of the methods. In this study we aimed to identify the frequency of EGFR T790M in NSCLCs before TKI treatment, comparing the detection rate of the three highly sensitive molecular methods.

Methods: Among 1100 NSCLCs (adenocarcinomas at stage IIIB or IV), we identified 130 NSCLCs with EGFR TKI-sensitive mutations, by MALDI-TOF mass spectrometry (MALDI-TOF MS) and MiSeq® Lung Status kit. The diagnostic performance in detecting neo-EGFR T790M in these 130 tumors was evaluated comparing three methods, namely MALDI-TOF MS, True Time AS-PCR (Easy™EGFR kit) and ddPCR™ (Quatro Droplet Digital PCR, PrimePCR™ Assays). Sensitivity and specificity of each method were defined by using a DNA reference standard set (Horizon). Limit of blank (LOB) of AS-PCR and ddPCR were determined by measuring replicates of 26 wild-type EGFR DNA samples obtained from peripheral blood lymphocytes and formalin-fixed paraffin embedded (FFPE) normal lung tissue.

Results: Comparison of the three methods was possible for 91 of the 130 NSCLCs. Overall, we identified a total of 16 de novo EGFR T790M in the analyzable tumors (18%). In detail, 4 cases were identified by MALDI-TOF MS and confirmed by AS-PCR and ddPCR. Two de novo mutated cases were additionally detected by AS-PCR, ddPCR confirmed EGFR T790M in all these tumors and additionally identified 10 mutated cases. Most of mutated cases showed a mutant-allele frequency between 5% and 0.1%. Titration experiments using a DNA reference standard set demonstrated higher sensitivity of ddPCR (0.1%) than AS-PCR (1%) and MALDI-TOF MS (5%). Analysis of wild-type EGFR DNA from FFPE samples was crucial for the determination of LOB of ddPCR in order to maximize sensitivity, avoiding loss of specificity.

Conclusions: In this study, 18% of TKI-naïve NSCLCs show EGFR T790M mutation together with an EGFR activating mutation. Most of mutated cases showed a mutant-allele frequency between 5% and 0.1%. ddPCR is a robust method enabling the detection of mutant-allele frequencies as low as 0.1%. However, a careful preliminary evaluation of the specificity of this test is mandatory, especially when FFPE tissues are investigated. Legal entity responsible for the study: Aast-Sette Laghi Ospedale di Circolo Varese Funding: AstraZeneca Disclosure: All authors have declared no conflicts of interest.

1338P A meta-analysis on epidemiology of ROS1 rearrangement in Asian and non-Asian population

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Background: ROS1 is now recognised as a definite molecular target in NSCLC.1 Studies showed that ROS1 positive patients are significantly younger & more likely to be non-smokers.2 Previous studies found epidermal growth factor receptor (EGFR) mutation in NSCLC was significantly higher in Asian population compared to non-Asian.3 Objective of the study is to evaluate the difference between epidemiological parameters of ROS1 rearrangements in Asian & non-Asian patients by performing meta-analysis.

Methods: We systematically searched databases like PubMed & E- journals since 2011. Statistical analysis for this study was done on 20 studies (11,665 patients) conducted globally & open source software R (version 3.3.2) was used for meta-analysis.

Results: Global prevalence of ROS1 rearrangement was 2% (95% CI: 0.016 - 0.026) it was higher in Asian (2.2% (95% CI: 0.016 - 0.029)) than non-Asian (1.9% (95% CI: 0.012 - 0.027)) (p = 0.92). Mean age of Asian & non-Asian was 54.5 yrs & 59 yrs respectively. The prevalence rate in non-Asian females, was significantly higher (3.8% (95% CI: 0.011 - 0.078)) than non-Asian males (0.7% (95% CI: 0.003 - 0.012)) (p = 0.003). Similarly, prevalence rate in Asian females (2.8% (95% CI: 0.019 - 0.038)) was higher than Asian males (2.1% (95% CI: 0.012 - 0.033)) (p = 0.88). Smokers in Asia were more likely to have ROS1 rearrangement (1.8% (95% CI: 0.005 - 0.037)) compared to non-smokers (0.6% (95% CI: 0.004 - 0.0152)) (p = 0.93). Wheres, prevalence rate amongst non-smokers in non-Asia (1.9% (95% CI: 0.039 - 0.110) was significantly higher than smokers (0.7% (95% CI: 0.002 - 0.007)) (p = 0.008). Clinical stage IV was more common in both population than other stages. In 5 out of 20 studies, ROS1 positivity was higher (3.12%-8%) in enriched (EGFR-wt/ALK-de) population (non-smokers 6% (95% CI: 0.046 - 0.083)) compared to overall population.

Methods: An ultrarobust ARMS-PCR assay for hotspot EGFRmut was established, with detection limits between 0.02% and 0.1%. A total of 134 plasma samples were prospectively analysed from 68 patients with metastatic lung adenocarcinoma at diagnosis or progression, recruited between Jan 13-Apr 17 from 5 centres. A total of 217 plasma samples were obtained with sampling of plasma EGFRmut till radiologic progression in one centre. We further evaluated the performance of ARMS-PCR assay, AmpliSeq Lung and Colon NGS assay and Oncomine Lung cDNA NGS assay in 29 NSCLC and 20 healthy plasma controls.

Results: Concordance rates between cDNA and tumor was 83.8%, with sensitivity 80.0%, specificity 94.4%, positive predictive value 97.6%, and negative predictive value 63.0%. Dynamic monitoring of plasma EGFRmut levels demonstrated rising levels a median of 2.1 months (1.9–3.9) before radiological progression. This detection also held true for tissue EGFRmut positive patients negative for plasma EGFRmut at entry study. 20 of 49 patients at progression were plasma T790M positive, and clinical benefit rates were 91.0% for osimertinib-treated patients. Evaluation of ARMS-PCR and NGS platforms yielded an overall concordance rate, sensitivity and specificity were 85.9%, 63.4%, 92.3% (ARMS-PCR), 87.2%, 47.8%, 100% (Ampliseq) and 84.1%, 83.1%, 87.4% (Oncomine).

Conclusions: ARMS-PCR provides a useful diagnostic and monitoring adjunct for NSCLC EGFRmut patients. Amplicon-based targeted next-generation sequencing approaches with error correction is a promising approach requiring additional validation.

Legal entity responsible for the study: Institute of Bioengineering and Nanotechnology

Funding: Agency for Science, Technology and Research (A*STAR) Disclosure: All authors have declared no conflicts of interest.

A large prospective cohort study of the clinical features of advanced lung cancer harboring HER2 aberrations (HER2-CS STUDY)


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Background: HER2 is a potential driver oncogene. HER2-targeted precision therapy has been tested in NSCLC. However, the demographics of HER2-positive NSCLC have not been defined systematically.

Methods: Pts with advanced NSCLC were registered. HER2-IHC and FISH assays were performed with commercial kits. HER2 mutations were identified by the direct sequencing. The aim of this study was to clarify the frequency, characteristics and outcome of HER2-positive NSCLC.

Results: Of 1,126 tumors screened (Table A), 34 (3.0%) were HER2+ and 34 (3.0%) were HER2+ /FISH+. Among the 724 EGFR wild-type tumors, 21 (2.9%) were HER2-mutant tumors, including A775_G776insYVMA (n = 15). Interestingly, the HER2+ tumors and mutant tumors were entirely exclusive. Female pts had HER2 mutant tumors more frequently, while IHC/FISH+ tumors were detected more often in males (Table B). HER2-positive tumors had similar survival outcome to triple negative tumors, but significantly worse prognosis than EGFR-mutant and ALK-positive tumors (p < 0.05 each).

Conclusions: This is the first prospective study showing a small fraction of NSCLC possessed HER2 aberrations. HER2-positive tumors had relatively poor prognosis. NSCLCs with HER2+ IHC+ and mutation seemed to be distinct subsets.

Clinical trial identification: UMIN registration number 000117003

Legal entity responsible for the study: HER2-CS Network

Funding: Japan Agency for Medical Research and Development


Transcriptomic analysis of bronchoalveolar lavage cells from advanced non-small cell lung cancer identifies overexpressed immunoglobulin genes of immunosuppressive implication


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Background: Diverse pattern of inflammatory cells infiltration in the microenvironment of non-small cell lung cancers (NSCLCs) has key implication for successful immunotherapeutic approaches (Gajewski et al. Nat Immunol 2013). However, study of these cells remains challenging particularly in advanced disease where tumor resect is never possible. We hypothesized that transcriptomic study of bronchoalveolar lavage (BAL) cells is useful in this setting to identify characteristic gene expression of immunological significance.

Methods: BAL cells were obtained from 13 patients of advanced NSCLC and 6 normal controls. In NSCLC group, lavage was performed from the lung segment where tumor was located. RNA was extracted and hybridized to Affymetrix HG-U133 plus2.
Assessing response to immunotherapy in patients with non-small cell lung cancer using circulating tumor DNA

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Background: Evaluation of response to immune checkpoint inhibitors by serial imaging can be complicated by the possibility of pseudo-progression or delayed response, sometimes resulting in discontinuation of an effective therapy or delay of alternate treatment. Monitoring tumor cell death by measuring changes in circulating tumor DNA (ctDNA) levels in blood may permit early assessment of immunotherapy efficacy.

Methods: We examined ctDNA levels in plasma samples from patients with metastatic non-small cell lung cancer (NSCLC) undergoing treatment with a PD-1 or PD-L1 inhibitor. ctDNA was quantified in plasma by determining the allele fraction of cancer-associated somatic mutations using a multi-gene next-generation sequencing assay. A ctDNA response was defined as more than 50% decrease in mutant allele fraction from baseline, with a second confirmatory measurement. Radiographic response assessment was performed using RECIST 1.1. Changes in ctDNA levels over time were correlated with imaging findings and with clinicopathologic outcomes.

Results: Twenty-eight patients with metastatic NSCLC had ctDNA quantified in serial blood samples collected before and during treatment with a PD-1 axis inhibitor. Strong agreement was observed between ctDNA response and radiographic response (Cohen’s Kappa = 0.753, P < 0.001). The median time to response was 24.5 days by ctDNA versus 72.5 days by imaging. Patients who had a ctDNA response remained on immunotherapy for a median of 203.5 days compared to a median of 69 days for those who did not have a ctDNA response (P < 0.001). Progression-free survival (PFS) and overall survival (OS) were significantly better for patients with vs. without a ctDNA response versus those without (hazard ratio [HR] for PFS, 0.29; 95% confidence interval [CI], 0.09-0.89; P = 0.03 and HR for OS, 17.95; CI, 0.05-0.62, P = 0.007).

Conclusions: An early drop in ctDNA levels enable assessment of response to immune checkpoint inhibitor therapies at a time when radiographic response may be uncertain for patients with metastatic NSCLC. Achievement of such a ctDNA response is predictive of a longer duration of therapeutic benefit as well as superior PFS and OS.

Legal entity responsible for the study: Yale University

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Funding: None.
Table: 1343P

<table>
<thead>
<tr>
<th>Type of 2nd-Generation TKI</th>
<th>Overall</th>
<th>Intracranial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N°</td>
<td>N°</td>
</tr>
<tr>
<td></td>
<td>Confirmed Responses, n (%)</td>
<td>Confirmed Responses, n (%)</td>
</tr>
<tr>
<td>Alectinib</td>
<td>33 (27)</td>
<td>16 (80)</td>
</tr>
<tr>
<td>Ceritinib</td>
<td>29 (31)</td>
<td>23 (81)</td>
</tr>
<tr>
<td>Brigatinib</td>
<td>6 (17)</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Other</td>
<td>5th</td>
<td>2 (40)</td>
</tr>
</tbody>
</table>

*Patients in each group of prior TKI, a patient could have received more than one type of prior TKI.

*Other TKIs included entrectinib (n = 3) and ensartinib (n = 2).

Conclusions: Lorlatinib has shown clinical activity in pts with ALK+ NSCLC who had received ≥1 prior 2nd-generation TKI.

Clinical trial identification: NCT017907665

Legal entity responsible for the study: Pfizer

Funding: Pfizer


Table: 1344P

Efficacy in ALK+ NSCLC Pts

<table>
<thead>
<tr>
<th></th>
<th>All n = 71</th>
<th>90 mg qd n = 13</th>
<th>90 mg → 180 mg qd n = 25</th>
<th>CRZ-Naive All n = 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>cORR, n (%), 95% CI</td>
<td>45 (63) 51–75</td>
<td>7 (54) 25–81</td>
<td>19 (76) 55–91</td>
<td>8 (100) 63–100</td>
</tr>
<tr>
<td>Median duration of response in confirmed responders, months, 95% CI</td>
<td>14.5 (9.0–26.1)</td>
<td>11.1 (3.8–16.7)</td>
<td>14.9 (7.9–33.3)</td>
<td>32.4 (5.6–NR)</td>
</tr>
<tr>
<td>Median PFS, months, 95% CI</td>
<td>13.2 (9.2–16.7)</td>
<td>11.9 (3.5–21.2)</td>
<td>16.3 (9.2–28.1)</td>
<td>34.2 (7.4–NR)</td>
</tr>
<tr>
<td>Probability of PFS at 1 year, %, 95% CI</td>
<td>53 (41–65)</td>
<td>50 (21–74)</td>
<td>62.40–78</td>
<td>75 (32–93)</td>
</tr>
<tr>
<td>Median OS, months, 95% CI</td>
<td>30.1 (21.4–NR)</td>
<td>21.2 (9.9–47.6)</td>
<td>29.5 (21.4–NR)</td>
<td>NR (NR–NR)</td>
</tr>
<tr>
<td>Probability of OS at 1 year, %, 95% CI</td>
<td>77 (65–85)</td>
<td>69 (37–87)</td>
<td>84 (63–94)</td>
<td>100 (100–100)</td>
</tr>
<tr>
<td>Probability of OS at 2 years, %, 95% CI</td>
<td>61.48 (−71)</td>
<td>46 (19–70)</td>
<td>64 (42–79)</td>
<td>100 (100–100)</td>
</tr>
</tbody>
</table>

*BRG regimes used in the pivotal phase 2 trial

CRZ-Naive: Crizotinib

Conclusions: Brigatinib (BRG) in anaplastic lymphoma kinase (ALK)-positive non–small cell lung cancer (NSCLC): Long-term efficacy and safety results from a phase 1/2 trial


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Background: The next-generation ALK inhibitor BRG has shown activity in ALK+ NSCLC patients (pts) in clinical trials.

Methods: Pts with advanced malignancies (N = 137, including 79 pts with ALK+ NSCLC) received oral BRG (30–300 mg/d) in a phase 1/2, open-label, multicenter trial (NCT01449461). We report activity by RECIST v1.1 in ALK+ NSCLC pts and safety in all pts, with long-term follow-up (>31 months since last pt was enrolled).

Results: Among 79 ALK+ NSCLC pts, median age was 54 years; 90% (71/79) had received prior crizotinib (CRZ). As of 21 Feb 2017, 32% of ALK+ NSCLC pts (25/79) and 39% (27/72) of those receiving 180 mg qd with a 7-day lead-in at 90 mg were evaluable in a phase 2 portion of the trial continued to receive BRG. Median treatment duration was 20.8 months (1 day to 56.1 months). Confirmed objective response rate (cORR) was 63% (45/71) in pts with prior CRZ and 100% (8/8) in CRZ-naive pts. Additional efficacy data are shown in the table. At 180 mg qd (with lead-in), confirmed cORR was 76% (95% CI, 59%–91%) and median progression-free survival (PFS) was 16.3 months (95% CI, 9.2–28.1) in pts with prior CRZ. Treatment-emergent adverse events (AEs) in ≥30% of all 137 pts, mostly grade 1/2, were nausea (55%), fatigue (45%), diarrhea (42%), headache (36%), and cough (34%). Grade ≥3 treatment-emergent AEs in ≥5% of pts were increased lipase (12%), pneumonia (7%), dyspnea (6%), and hypertension (6%). Eleven percent of pts (15/137) discontinued BRG due to an AE.

Conclusions: BRG shows major antitumor activity in ALK+ NSCLC pts with an acceptable safety profile in this long-term follow-up. PFS of ≥16 months in pts receiving 180 mg qd with a 7-day lead-in at 90 mg is among the longest reported in CRZ-resistant ALK+ NSCLC. This dosing regimen is being investigated in a randomized phase 3 trial of BRG vs CRZ in ALK inhibitor–naive pts with advanced ALK+ NSCLC (ALTA-1L, currently recruiting pts).


Legal entity responsible for the study: ARIAD Pharmaceuticals, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

Funding: ARIAD Pharmaceuticals, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

Background: The CNS is often a site of first disease progression in CRZ-refractory ALK-positive non-small cell lung cancer (NSCLC) and baseline brain metastases

Methods: ALTA (NCT02094573) permitted baseline CNS disease (including pts with prior whole brain radiotherapy/sterotactic radiosurgery and asymptomatic untreated pts). 222 pts stratified by presence of brain metastases and best response to prior CRZ were randomized 1:1 to receive BRG 90 mg qd (arm A, n = 112) or 180 mg qd with a 7-day lead-in at 90 mg qd (arm B, n = 110). This analysis included an exploratory competing risks analysis to estimate cumulative incidence of CNS progression vs non-CNS progression - death in pts with baseline brain metastases.

Results: 80 (71%/73%) (66%) in arm A had baseline brain metastases per independent review committee (median age, 49/55 years; 76%/74% had received chemotherapy). As of 21 Feb 2017, median follow-up for pts with brain metastases was 17.7 months; 34%/40% continued to receive BRG in A/B. Table shows intracranial efficacy: 5 pts with measurable baseline brain metastases in A had progression in the brain (≥20% growth in target lesions or new lesions) while receiving BRG 90 mg qd and escalated to 180 mg qd with ≥3 additional scan; all 5 had a reduction in measurable lesions after escalation (≥14% to ≥100%). While pts without baseline brain metastases did not have routine brain MRI scans, 3/32 and 1/36 pts without baseline brain metastases per investigators in A and B, respectively, had a new brain lesion identified by MRI.

Conclusions: In this update of ALTA, BRG continued to show robust intracranial efficacy in ALK+ NSCLC pts with baseline brain metastases, particularly at 180 mg (with lead-in), with a higher intracranial response rate and a numerically lower incidence of disease progression in the CNS and outside the CNS, compared to 90 mg.

<table>
<thead>
<tr>
<th>Table: 1345P</th>
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<tbody>
<tr>
<td>Arm A</td>
</tr>
<tr>
<td>confirmed ORR (pts with measurable brain metastases), n (%)</td>
</tr>
<tr>
<td>confirmed ORR (pts with measurable, active* brain metastases), n (%)</td>
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<tr>
<td>median duration of intracranial response* (pts with measurable brain metastases), months (95% CI)</td>
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<tr>
<td>median PFS (pts with any baseline brain metastases), months (95% CI)</td>
</tr>
<tr>
<td>competing risks analysis</td>
</tr>
<tr>
<td>CIR of first disease progression in CNS, % (95% CI)</td>
</tr>
<tr>
<td>By 12 months</td>
</tr>
<tr>
<td>By 18 months</td>
</tr>
<tr>
<td>CIR of first disease progression at non-CNS site, % (95% CI)</td>
</tr>
<tr>
<td>By 12 months</td>
</tr>
<tr>
<td>By 18 months</td>
</tr>
<tr>
<td>CIR of death prior to all disease progression (in CNS or at non-CNS site), % (95% CI)</td>
</tr>
<tr>
<td>By 12 months</td>
</tr>
<tr>
<td>By 18 months</td>
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</table>

Pts with baseline brain metastases are shown, in these pts, CNS disease was tracked by MRI every 8 weeks. Last scan date: 28 Feb 2017 ALK+ NSCLC, anaplastic lymphoma kinase–positive non-small cell lung cancer, BRG, brigatinib; CI, confidence interval; CIR, cumulative incidence rate; CNS, central nervous system; CRZ, crizotinib; ORR, intracranial objective response rate; PFS, intracranial progression-free survival; IRC, independent review committee; MRI, magnetic resonance imaging; NR, not reached, pts, patients

Funding: ARIAD Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceuticals Company Limited.

Clinical trial identification: NCT02094573 First received by ClinicalTrials.gov: March 18, 2014

Legal entity responsible for the study: ARIAD Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

Funding: ARIAD Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

Disclosure: S.H. Ou: Honoraria (ARIAD, AstraZeneca, Novartis, Pfizer, Roche), consulting or advisory role (ARIAD, AstraZeneca, Novartis, Pfizer, Roche), speakers bureau (AstraZeneca, Roche), research funding (ARIAD, AstraZeneca, Clovis Oncology, Daiichi Sankyo, Ignyta, Novartis, Pfizer, Roche). M. Tiscia: Consulting or advisory role (AstraZeneca, BMS, Boehringer Ingelheim, Eli Lilly, Novartis, Onyx, Pierre Fabre), research funding (ARIAD). R. Camidge: Honoraria (ARIAD), research funding (ARIAD). V.M. Rivera, D. Kerstein: Employment, stock and other ownership interests (ARRA). V. Ingelholm, C. Stein: Employment, stock and other ownership interests (ARRA). M-J. Ahn: Honoraria (AstraZeneca, BMS, Boehringer Ingelheim, Eli Lilly, Novartis, Otsuka, Pierre Fabre), consulting or advisory role (ARRA, Blueprint Medicines, Daiichi Sankyo, EMD Serono, Ignyta, Novartis, Pfizer, Roche). S. Hwu, D. Kerstein, Y. Loh: Employment, stock and other ownership interests (ARRA). M. Awe: Employment, stock and other ownership interests (ARRA). All other authors have declared no conflicts of interest.
Background: Alectinib has shown central nervous system (CNS) activity in phase II trials of previously treated ALK+ NSCLC. We report CNS efficacy data from the phase III ALUR study (NCT02604342) of alectinib vs chemotherapy (CT) in pts with ALK+ NSCLC previously failed platinum-based doublet CT and crizotinib.

Methods: Pts aged ≥18 years with ALK+ NSCLC, previously treated with CT and crizotinib were randomised 2:1 to alectinib (600mg twice daily) or CT (pemetrexed 500mg/m²/C21; CT n=18 years with measurable CNS mets (alectinib n=26; C-ITT); 40 had measurable CNS mets (CT n=24). CNS outcomes were CORR in pts with measurable and non-measurable CNS mets (CT); 6-month cumulative incidence rate in the ITT, and C-ITT; CNS duration of response (CDOR) and disease control rate (CDCR); and safety.

Results: In total, 107 pts were randomised (alectinib n=72; CT n=35; ITT) of whom 76 had BL NSCLC disease (alectinib n=50; CT n=26; C-ITT); 40 had measurable CNS mets (alectinib n=24; CT n=16; mC-ITT) and 36 had non-measurable CNS mets (alectinib n=26; CT n=10; mC-ITT). CNS efficacy endpoints are shown in the Table. The 6-month cumulative incidence rate of CNS PD was 11% (alectinib) vs 48% (CT) in the ITT, 15% vs 52% in the C-ITT and 0% vs 39% in pts without BL CNS disease. Safety and tolerability profile compared favourably for alectinib vs CT.

Conclusions: CNS-related outcomes were significantly improved with alectinib vs chemotherapy in previously treated ALK+ NSCLC. Alectinib reduces CNS PD and prevents development of new CNS mets.

Clinical trial identification: NCT02604342

Legal entity responsible for the study: F. Hoffmann-La Roche Ltd.

Funding: F. Hoffmann-La Roche


Table: 1346P CNS efficacy endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Alectinib N = 76</th>
<th>Chemotherapy N = 26</th>
</tr>
</thead>
<tbody>
<tr>
<td>CORR, % (95% CI)</td>
<td>36 (0.001)</td>
<td>0 (0.001)</td>
</tr>
<tr>
<td>Difference (95% CI) P value</td>
<td>36% (13%-57%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CDOR, months (95% CI)</td>
<td>NE (6.2–NE)</td>
<td>0 (NE–NE)</td>
</tr>
<tr>
<td>CDOR, %</td>
<td>80</td>
<td>79.2</td>
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NE, not evaluable

Table: 1347P ALK-I Treatment Patterns

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Initial ALK-I (N=47)</th>
<th>Second ALK-I (N=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Time to RECIST PD</td>
<td>10.1 months (range 0.3–NR)</td>
<td>4.8 months (range 0.5–NR)</td>
</tr>
<tr>
<td>Pts continuing ALK-I beyond PD</td>
<td>17/47 (36%)</td>
<td>8/26 (30%)</td>
</tr>
<tr>
<td>Median duration of treatment beyond progression</td>
<td>5.0 (range 0.6–30 NR)</td>
<td>3.9 (range 1.3-21.5)</td>
</tr>
</tbody>
</table>

NR: not reached.
Conclusions: Treatment beyond disease progression for patients with advanced lung cancer harboring ALK rearrangement is common and is often associated with maintenance of symptom burden.

Legal entity responsible for the study: UHN, University of Toronto

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Overall survival (OS) in patients (pts) with EGFR T790M-positive advanced NSCLC: Results from two phase II studies


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Methods: With pts centrally confirmed T790M-positive (by cobs 4 EGFR Mutation Test) advanced NSCLC, who had progressed following 1st-line TKI treatment, received osimertinib 80 mg once daily. Other inclusion criteria were measurable disease, WHO performance status 0/1 and acceptable organ function. Pts with stable CNS metastases were eligible. The primary efficacy endpoint was objective response rate (ORR) by RECIST 1.1 per blinded independent central review (BICR). Secondary endpoints included duration of response (DoR), progression-free survival (PFS), OS and safety.

Results: As of the 1 Nov 2016 data cut-off (DCO) 411 pts had received osimertinib (129 pts as second-line and 282 pts as ≥3rd-line); median treatment exposure was 16.4 months (mo; range 2.9–7.9 mo). Pooled results (BICR) were: ORR: evaluable (for response set; EFR), 66% (95% confidence interval [CI] 61, 70); median DoR (EFR), 66% (95% confidence interval [CI] 61, 70); median OS in the second-line and later discontinued it, 2nd-line therapy was given in 394 (71%) pts and consisted of platinum-based CT for 252 (46%), single-agent CT for 97 (18%), and consisted of platinum-based CT for 252 (46%), single-agent CT for 97 (18%), 1st-generation EGFR TKI for 49 (9%) and other tx for 54 (10%) pts. Median time on 2nd-line tx was 2.9 months for platinum-based and 1.4 months for single-agent CT, with no relevant difference between Del19 and L858R mutation subgroups. Among 186 (34%) pts who received 1st-generation EGFR TKIs post-afatinib, median time on osimertinib was 9 months. Of 212 pts randomised to 1st-line CT in LL3 and LL6, 117 (55%) received 1st-line CT in the LL3/6/7 trials. Methods: We retrospectively assessed subsequent therapy outcomes in pts with common EGFR mutations, who were randomised to 1st-line afatinib in the LL3/6/7 trials. Data had been prospectively collected as study follow-up information. Tx duration was assessed by descriptive medians or KM estimates. Biases at afatinib resistance were not required in LL3/6/7.

Results: Of the 553 pts with common EGFR mutations who received 1st-line afatinib and later discontinued it, 2nd-line therapy was given in 394 (71%) pts and consisted of platinum-based CT for 252 (46%), single-agent CT for 97 (18%), 1st-generation EGFR TKI for 49 (9%) and other tx for 54 (10%) pts. Median time on 2nd-line tx was 2.9 months for platinum-based and 1.4 months for single-agent CT, with no relevant difference between Del19 and L858R mutation subgroups. Among 186 (34%) pts who received 1st-generation EGFR TKIs post-afatinib, median time on osimertinib was 9 months. Of 212 pts randomised to 1st-line CT in LL3 and LL6, 117 (55%) received 1st-line CT in the LL3/6/7 trials.

Conclusions: The majority (71%) of pts who received 1st-line afatinib were fit enough to receive subsequent therapies and there was no relevant difference in 2nd-line tx duration by Del19/L858R EGFR mutation subgroups. Introduction of a different TKI was common, with good outcome. Time on tx with osimertinib after afatinib was unexpectedly long among 34 pts; this should be examined in a larger cohort. Overall, these findings suggest that pts treated with 1st-line afatinib are well suited for subsequent therapies, including CT, 1st-generation EGFR TKIs and osimertinib.

Clinical trial identification: LUX-Lung 4, NCT01849650; LUX-Lung 6, NCT01212393; LUX-Lung 7, NCT01466660

Legal entity responsible for the study: Boehringer Ingelheim

Funding: Boehringer Ingelheim

Disclosure: L. Seguit, Employee of Boehringer Ingelheim, AstraZeneca, Novartis, Clovis, Genentech, Merrimack, Ariad, BMS, M. Schuler: Advisory boards for AZ, BI, Celgene, Eli Lilly, Novartis; corporate-sponsored research for BI, BMS, Novartis; honoraria from AZ, BI, BMS, Celgene, Eli Lilly, Novartis, Roche, AZ, MSD, Alexion; patents with University Duisburg-Essen. T. Kato: Consultant fees from AstraZeneca, BI, Chugai, Eli Lilly, MSD, Novartis; research grants for Chugai Pharmaceutical, Kirin Kyowa, Ono,摞 Merck Serono. H. Tanaka: Advisory board: AstraZeneca, Boehringer Ingelheim, Pfizer, Clovis Oncology, Astellas Pharma. K. Park: Advisory boards for AstraZeneca, BI, Chugai, Eli Lilly, MSD, Novartis, Ono, Boehringer Ingelheim, Novartis, Pfizer, Chugai, Eli Lilly; corporate-sponsored research for BI, BMS, Novartis, Pfizer, Chugai, Eli Lilly; corporate-sponsored research for BI, BMS, Novartis, Pfizer, Chugai, Eli Lilly; corporate-sponsored research for BI, BMS, Novartis, Pfizer, Chugai, Eli Lilly; corporate-sponsored research for BI, BMS, Novartis, Pfizer, Chugai, Eli Lilly; corporate-sponsored research for BI, BMS, Novartis; corporate-sponsored research for GlaxoSmithKline; K/AstraZeneca; K/Kyowa Hakko Kirin Co Ltd/Phizer Japan Inc./AbbVie Inc./Novartis Pharma K.K./Pfizer Boehringer Ingelheim Co Ltd/ Daiichi Sankyo Co Ltd./Eli Lilly Japan K.K./Ono Pharmaceutical Co Ltd/Ono Pharmaceutical Co Ltd./Yakuhi Honsha Co Ltd./PAREXEL International Corp/Ono Pharmaceutical Co Ltd./Janssen Pharmaceutical Companies LLC/Regeneron Pharmaceuticals Inc. N. Yamamoto: Ad boards: AZ, BI, Chugai, Eli Lilly, MSD, Novartis, Ono, Taiho Pharmaceutical; Bi or corporate-sponsored research: BI, Chugai, Eli Lilly, MSD; Honoraria: AZ, BI, Chugai, Eli Lilly, MSD; Ono, Taiho, K. Nakagawa: Advisory board: Astellas Pharma Inc./Eli Lily Japan K.K./Ono Pharmaceutical Co Ltd./Novartis Pharmaceuticals K.K./Novartis Pharmaceuticals K.K./Tanabe Pharamaceuticals Co Ltd./Eli Lilly Japan K.K./Mitsubishi Chemical Pharma Co Ltd./Mitsubishi Tanabe Pharma Co Ltd./Mitsubishi Tanabe Pharma Co Ltd./Yakuhi Honsha Co Ltd./PAREXEL International Corp/Ono Pharmaceutical Co Ltd./Yakuhi Honsha Co Ltd./PAREXEL International Corp/Ono Pharmaceutical Co Ltd./Janssen Pharmaceutical Companies LLC/Regeneron Pharmaceuticals Inc.
Phase I study of TAS-121, a novel third-generation epidermal growth factor receptor (EGFR) inhibitor, in patients with EGFR mutation-positive non-small-cell lung cancer (NSCLC)

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Background: TAS-121 is an orally available, potent, novel epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) selectively targeting EGFR activating and T790M resistance mutations. This first-in-human phase I study evaluated the maximum tolerated dose (MTD), safety, tolerability, pharmacokinetics (PK), and antitumor activity of TAS-121.

Methods: The study was conducted in Japan and consisted of three phases: dose escalation phase (DEP), expansion phase first stage (EPI), and second stage (EPI2). Patients were eligible for inclusion in the study if they had advanced EGFR-mutation-positive non-small-cell lung cancer (NSCLC) and were previously treated with a first or second-generation EGFR-TKI or both. The central confirmation of EGFR T790M mutation in plasma circulating cell-free DNA or tumor tissue or both was required for enrollment in the EPI phase.

Results: A total of 127 patients received 4-16 mg TAS-121 dose once daily (QD) or 8-12 mg daily in two divided doses (BID). The most common adverse drug reactions (ADRs) were platelet count decreased (66.9%), pyrexia (44.9%), and rash (37.8%). Other notable ADRs were interstitial lung disease (ILD) (7.9%) and pulmonary embolism (7.1%). All ILD incidences were grade 1. A total of 25 patients were on TKIs at baseline. In 25.0 and 44.4% of patients (4/16 and 8/18) administered 8 mg QD and BID, respectively. Confirmed objective responses according to the independent central review were observed in 25.0 and 44.4% of patients (4/16 and 8/18) administered 8 mg QD and BID, respectively. Furthermore, in the EPI group, 37.0% of patients showed confirmed objective responses according to the independent central review. The overall response rate was 21.5% (9/42). Other AEs included grade 3/4 laboratory abnormalities (37.8%) and grade 3/4 treatment-related deaths occurred during the study. Dose-limiting toxicities (DLTs) were observed in five and three patients treated QD (drug-induced liver injury, platelet count decreased, urticaria, and ILD) and BID (ILD, platelet count decreased, and left ventricular failure), respectively. The MTD was determined as 10 mg QD and 8 mg BID. PK analyses showed that the area under the curve (AUC) of TAS-121 even at the lowest dose was significantly higher than that of the effective dose in preclinical tumor xenograft model. Furthermore, in the EPI group, confirmed objective responses according to the independent central review were observed in 25.0 and 44.4% of patients (4/16 and 8/18) administered 8 mg QD and BID, respectively.

Conclusions: TAS-121 was well tolerated up to the MTD and demonstrated antitumor activity in this preliminary phase I study in patients with EGFR T790M mutation-positive NSCLC.

Clinical trial identification: JapICIT-142651

Legal entity responsible for the study: Taiho Pharmaceutical Co., Ltd

Funding: Taiho Pharmaceutical Co., Ltd


The addion of apatinib to gefitinib or icotinib for advanced non-small cell lung cancer with acquired resistance to first-generation epidermal growth factor receptor tyrosine kinase inhibitor: An assessment of effectiveness and safety


Background: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have been proved as an effective treatment of advanced non-small-cell lung cancer patients with EGFR mutations. However, resistance to EGFR-TKIs develops in most patients and leads to eventual loss of efficacy. Nowadays combined therapy inhibiting EGFR and vascular endothelial growth factor (VEGF) pathways has become a promising therapy in the treatment of advanced non-small-cell lung cancer. This study aims to assess the efficacy and safety of the combination of AstraZeneca’s apatinib, one of TKIs targeting vascular endothelial growth factor receptor 2 (VEGFR-2), to first-generation EGFR-TKIs for advanced non-small cell lung cancer with acquired resistance to first-generation EGFR-TKIs.

Methods: We retrospectively assessed the efficacy and safety of patients with non-small-cell lung cancer who had gradual progression after experiencing effective targeted therapy with first-generation EGFR-TKIs. Patients received apatinib 250 mg once daily and gefitinib/250mg once daily or icotinib 125mg three daily until disease progression again or unacceptable toxicity occurs.

Results: The study group comprised 31 Chinese patients, among whom 15 (48.3%) were males and 16 (51.7%) were non-smokers. The median duration of combined therapy was 5.5 months. 17 patients (54.8%) had a partial response (PR) and 13 patients had stable disease (SD). The overall response rate was 51.5% (15/29) of all adverse events were observed in this study. The incidence of severe adverse events was only 0.3%. The incidence of adverse events in patients decreased in hypertension, rash, proteinuria, hand-foot syndrome, gastrointestinal reaction, mucosal inflammation, bleeding, ala- nine aminotransferase increased and hypoovarianism.

Conclusions: The addition of low dose of apatinib to gefitinib or icotinib can significantly inhibit tumour growth and improve the progression-free survival of patients received first-generation EGFR-TKIs. Potential advantage in safety should be clarified which warrant further validation.

Legal entity responsible for the study: None

Funding: None

Disclosure: All authors have declared no conflicts of interest.
On the other hand, without TKIs, OS after BM with LMCc (4.9m) was extremely worse in LMCc cases, but LMCc was still a significant risk factor of CNS death even with TKIs (HR: 1.16, 95% CI 1.07, 1.27, P = 0.002, respectively). TKI had decreased the incidence of CNS death from 100% to 64% in LMCc cases, but LMCc was still a significant risk factor of CNS death even with TKIs (OR: 3.95 and 6.26, P = 0.148 and 0.002, respectively). TKI had decreased the incidence of CNS death from 100% to 64% in LMCc cases, but LMCc was still a significant risk factor of CNS death even with TKIs (OR: 3.95 and 6.26, P = 0.148 and 0.002, respectively).

Conclusions: CNS response to osimertinib in Asian-Pacific patients (pts) with T790M-positive advanced NSCLC: data from an open-label Phase II trial (AURA17)

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Background: Osimertinib has shown CNS efficacy in a pooled analysis of two Phase II trials (AURA extension: NCT01802632, AURA2: NCT02094261) in pts with T790M-positive advanced NSCLC. We report osimertinib efficacy in CNS metastases (nets) from a Phase II, open-label, single-arm trial (AURA17: NCT02442349) in Asian-Pacific pts with T790M-positive advanced NSCLC who had progressed on prior EGFR-TKI therapy, with or without additional anti-cancer regimens.

Methods: Pts with stable, asymptomatic, CNS nets were eligible for enrolment and received osimertinib 80 mg once daily. This prespecified subgroup analysis was conducted in pts with CNS nets present on baseline brain scan as assessed by blinded independent central neuroradiology review (BICR). Endpoints included CNS objective response rate (ORR), duration of response (DoR) and progression-free survival (PFS) by RECIST 1.1. The CNS full analysis set (fAS) comprised pts with ≥1 measurable and/or non-measurable CNS lesion present on baseline brain scan by BICR; the CNS evaluable for response set (cEFR) comprised pts with ≥1 measurable CNS lesion.

Results: At the data cut-off of 4 November 2016, 391/717 (55%) pts were included in the fAS. In the fAS and cEFR (n = 23), 3 and 0 pts had brain radiotherapy ≤6 months prior to study entry, respectively. CNS ORR was 36% (95% CI 27.7, 44.9) in the fAS and 42% (25.9% 53% 36.56) for the cEFR. Median CNS DoR was not reached (95% CI 9.2, not calculable [NC]) for the fAS and 11 months (95% CI 8.2, NC) for the cEFR. CNS PFS was 85% (95% CI 77, 92) for the fAS and 91% (95% CI 72, 94) for the cEFR. Median CNS PFS was not reached in both fAS (95% CI 12.4, NC) and cEFR groups (95% CI 4.4, NC), with a median follow-up for CNS PFS of 7.1 and 8.2 months, respectively. At 12 months, 79% (95% CI 53, 82) of pts in the fAS and 61% (95% CI 31, 81) of pts in the cEFR were estimated to remain on study, alive and progression-free.

Conclusions: These data are consistent with previous reports of CNS response to osimertinib in pts with T790M-positive advanced NSCLC in global studies, and demonstrate clinically meaningful efficacy in Asian-Pacific pts with CNS nets. Clinical trial identification: NCT02442349

Legal entity responsible for the study: AstraZeneca

Funding: AstraZeneca

Disclosure: C. Zhou: Lecture honorarium: Eli Lilly, AZ, Roche, Pfizer, Sanofi, BI, Henrun Advisory board: Roche, BI, AZ. Y. Lu: Consulting or Advisory Role: AstraZeneca, Hoffmann-La Roche, Eli Lilly, Pfizer, Elekta, Varian Medical Systems. J. Wang, Y. Chen: Employee of AstraZeneca. Y-L. Wu: Speaker fees from AstraZeneca, Roche, Eli Lilly, Sanofi, Pfizer. All other authors have declared no conflicts of interest.

1345P

Osimertinib in Asia-Pacific patients (pts) with T790M-positive advanced NSCLC: Updated Phase II study results including progression-free survival (PFS)

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Background: Osimertinib is an oral, potent, CNS active, irreversible EGFR-TKI selective for EGFR-TKI sensitising and T790M resistance mutations. AURA17 (NCT02442349) is a Phase II, open-label, single arm study investigating the safety and efficacy of osimertinib in Asia-Pacific pts with T790M-positive advanced NSCLC, who had progressed on prior EGFR-TKI therapy, with or without additional anti-cancer regimens.

Methods: Eligible pts had measurable disease, WHO performance status 0/1 and acceptable organ function; asymptomatic CNS metastases were allowed. T790M-positive status was confirmed by central testing of biopsy samples using the cobas EGFR Mutation Test. Osimertinib 80 mg was administered orally once daily until disease progression. The primary endpoint was objective response rate (ORR) according to RECIST 1.1 by blinded independent central review. Secondary endpoints included duration of response (DoR), PFS, disease control rate (DCR), overall survival, safety and tolerability.

Results: As of 4 Nov 2016 data cut-off (DCO), 171 pts had received osimertinib (53% [31%] second-line; 118 [69%] third-line), median treatment exposure was 12.3 (range 0.2–14.6) mo. Median age 60 (range 26–82) years; female 68%; Chinese ethnicity 87%; never smokers 78%; EGRX 19 deletion 64%; EGFR L858R mutation 35%; CNS metastases at study entry 35%. Confirmed ORR in pts evaluable for response (n = 166) was 63% (95% confidence interval [CI] 55, 70) and DCR was 89% (95% CI 83, 93). Median DoR was 9.9 mo (95% CI 8.3, not calculable). Median PFS in the full analysis set (n = 171) was 7.9 mo (95% CI 7.0, 11.1); 94% (95%) had progression at DCO, 39 pts had died (23%). All causality adverse events (AEs) of CTCAE Grade ≥3 were reported by 43 (25%) pts. Most common AEs were diarrhoea 35% (Grade ≥3) and rash grouped term 2% (Grade ≥3). There was one reported case of interstitial lung disease and pneumonitis, respectively.

Conclusions: The high ORR of 63% was supported by the durable response assessed by DoR (median 9.9 mo) and PFS (median 9.7 mo). The efficacy data were consistent with global clinical trials of osimertinib. No new safety signals were observed.

Clinical trial identification: NCT02442349

Legal entity responsible for the study: AstraZeneca

Funding: AstraZeneca

Disclosure: C. Zhou: Lecture honorarium: Eli Lilly, AZ, Roche, Pfizer, Sanofi, BI, Henrun AR: Roche, BI, AZ Y. Chen: AstraZeneca employee. X. Huang: I am an employee of AstraZeneca. M. Cantarini: Employee and shareholder of AstraZeneca. Y-L. Wu: Speaker fees from AstraZeneca, Roche, Ili Lilly, Sanofi, Pfizer. All other authors have declared no conflicts of interest.
Methods: A global NPU program included patients with advanced NSCLC who had progressed after clinical benefit on prior erlotinib/gefitinib, had an activating EGFR or HER2 mutation, had exhausted all other treatment options, and were ineligible for afatinib trials. Pts received daily oral afatinib (starting dose 40/50 mg). Collection of safety data was mandatory. Time to treatment failure (TTF) was defined as time from start of afatinib treatment to the date of treatment discontinuation.

Results: As of May 2017, data were available for 28 pts with HER2m+ NSCLC (male/female: 12/16 [43%]); median age: 55 yrs; starting dose 40/50 mg; 17/11 [61/39%]. Pts were heavily pretreated; 16 (57%) received afatinib as ≥4th-line treatment and 7 (25%) had received prior targeted-HER2 treatment. Median TTF for afatinib, calculated for all 28 patients was 2.9 months and, notably, 9 (32%) pts had TTF >1 yr. Response assessments were reported for 16 pts; disease control rate was 69% (11/16 pts) and objective response rate was 19% (3/16 pts). No new or unexpected safety findings were observed.

Conclusions: This analysis of a heavily pre-treated pt population with HER2m+ NSCLC from the afatinib NPU program showed a promising 32% of pts with TTF >1 yr, durable disease control and a manageable safety profile. With the limitation of retrospective analysis, our data support the need to explore whether the discordance in TTF between HER2 and EGFR mutants than can display different treatment sensitivities, these findings suggest that the evaluation of afatinib in earlier treatment lines in HER2m+ NSCLC pts may be warranted.

Legal entity responsible for the study: Boehringer Ingelheim

Funding: Boehringer Ingelheim

Disclosure: Y. Shih: Advisory board: AstraZeneca, Roche, Boehringer Ingelheim, MSD Oncology, Chugai Pharma. Honoraria: AstraZeneca, Roche, Eli Lilly, Boehringer Ingelheim, Pfizer, MSD Oncology, Bristol-Myers Squibb, Novartis. Other substantive relationship: Travel, Accommodations, Expenses: Roche, Boehringer Ingelheim, Bristol-Myers Squibb, V.W.Y. Liao: Honoraria: AstraZeneca, Roche,SiFer,Boehringer Ingelheim, Novartis, Eli LIfy, Merck Sharp & Dohme, Sanofi. S. V. Spataro: Advisory board: Roche, Novartis, Bristol-Myers, MSD, R. Lorence: Employee and consultant for Boehringer Ingelheim Pharmaceuticals, Inc. A. Cach: Employee of Boehringer Ingelheim. All other authors have declared no conflict of interest.

Octogenarians with EGFR-mutated non-small cell lung cancer (NSCLC) treated by Tyrosine Kinase Inhibitor (TKI): A multicentric real world study assessing tolerance and efficacy. OCTOMUT study GFPC 07-15

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Background: Tyrosine kinase inhibitors (TKI) are the standard of treatment in first line for advanced EGFR-mutated NSCLC. few data exist about their tolerance and efficacy in octogenarians particularly in Caucasian population. The purpose of this multicentric real world study was to assess tolerance and efficacy of EGFR-TKI in this population.

Methods: We retrospectively identified patients aged 80 years or older with EGFR-mutated NSCLC treated by EGFR-TKI between 01/2012 and 03/2015 whatsoever the line of treatment. Patients were described according to their clinical characteristics, management and outcomes (progression-free survival (PFS) and overall survival (OS)).

Results: The 20 french participating centers included 114 patients: 77% were women, the median age was 89.5 ± 3.9 years. 98.2% were Caucasians and 84.6% were home life (45% had home help), 71% took more than 5 drugs/d. Respectively 64%,17.5% and 8.5% of patients had a performance status of 0-1/2/3 at diagnosis. 76% of them were nonsmokers, 95.6% had adenocarcinomas. 80%/13%/7% had respectively stage IV/III/I-1 at treatment initiation. EGFR mutations were identified on exon 19 (46.5%), exon 21 (40.3%), exon 20 (5.2%). A geriatric assessment was assessed in 35% of cases. Median time between first symptoms and diagnosis was 55 days. 97.3% of the patients were treated by TKI as first or second line. Median PFS was 11.9 months, 95% CI 8.6-14.7. Response and disease control rates were 67% and 79% respectively. In 40% of the cases.GER-TKI treatment was maintain beyond progression. After progression, 44.7% of patients received the another line of treatment (chemotherapy 44.7%). Median OS was 20.9 months, 95% CI 14.3-27.1. Main toxicities were cutaneous: 66% (grade 3/4: 14%); diarrhoea 56% (grade 3/4: 15%, grade 5: 2%); others 25.6% (grade 3/4: 41%).

Conclusions: In this real-world analysis, compared to younger patients, octogenarians patients with EGFR-mutated NSCLC treated by EGFR-TKI present comparable outcomes and also considering that different NSCLC from the afatinib NPU program showed a promising 32% of pts with TTF >1 yr, durable disease control and a manageable safety profile. Therefore, to evaluate the relationship between erlotinib exposure and efficacy, we conducted this prospective study.

Methods: Erlotinib was orally administered at a dose of 150 mg/body once daily to patients with NSCLC, who were not previously treated with EGFR-TKIs. A series of blood samples were taken at predetermined times on day 1 to calculate the area under the concentration-time curve (AUC). Erlotinib trough concentrations (C_{trough}) at each visit and the level of alpha-1 acid glycoprotein (AAG), which is a binding protein of erlotinib in serum, were measured.

Results: Of 70 patients enrolled, 61 had activating EGFR mutations (30 patients with exon 19 deletions and 31 with exon 21 L858R mutations). The AUC was 37.0 μg/mL in median (range: 9.7-63.5). Objective response rate and median progression-free survival (PFS) were 72% and 12.4 months in the patients with EGFR activating mutations. Response was not associated with AUC. There was also no significant difference in PFS between patients with AUC > 37.0 μg/mL and ≤ 37.0 μg/mL. C_{trough} was significantly correlated with the grade of skin rash (p < 0.01), but not with objective response. In multivariable analyses, pretreatment AAG level, which was 0.97 g/L in median (0.53-3.83), was found to be a significant factor in PFS for patients with EGFR-activating mutations (median PFS, AAG > 0.97 g/L: 7.9 months; AAG ≤ 0.97 g/L: 16.8 months, p < 0.01).

Conclusions: The lack of a relationship between erlotinib exposure and efficacy shows that the approved dose of erlotinib is sufficient to reach the therapeutic range in EGFR-activating mutant NSCLC, even with dose reduction due to toxicities. AAG level can be a prognostic factor for patients with NSCLC harboring EGFR-activating mutations treated with erlotinib.

Clinical trial identification: UMIN000012862 (16-Jan-2014)

Legal entity responsible for the study: Shuzoku Cancer Center

Funding: This study was conducted by ISPS KAKEN Grant

1359P Impact on OS and PFS of 2nd and 3rd generation TKI in EGFR m+ and ALK+ pts: Results of the NWEOL network

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Background: Clinical research data shows that early mutation testing for pts with NSCLC stage IV could lead to an effective choice of therapy for pts with proven mutation. Targeted therapies achieve a higher ORR, OS, PFS and a better quality of life than chemotherapy in mt+ pts. With the advent of 2nd and 3rd generation TKI&inactives effective in 1st generation TKI resistant tumors, we wanted to study the impact of these drugs on the outcome of pts in a real life setting.

Methods: 1381 pts from three cancer centers diagnosed with non-squamous cell NSCLC stage IV (UICC 7) were examined. Methods for the mutation testing was performed according to the German Oncopedia guidelines using either Sanger Sequencing or COBAS® or Next Generation Sequencing (hybrid capture NGS, New Oncology Cologne).

Results: 879/1381 (64%) consecutive pts with non-squamous cell NSCLC from three cancer centers were studied for the presence of tumor mutations, especially for EGFR and ALK mt+. The EGFR mt+ rate was 16.6% (141/847), and the ALK-translocation rate 3.8% (24/635). Median OS in EGFR mt+ pts was 28 (n = 79) vs 28 (n = 38) vs 16 (n = 14) months respectively (center 1 vs center 2 vs center 3). Median OS in ALK mt+ pts was 24 months (n = 17) in center 1 and 11 months (n = 5) in center 2 (p = 0.033). The ORR in the CR/PR group was 54.2% for pts treated with chemotherapy and 77% for pts treated with TKI on 1 line therapy. The chance to reach a CR/PR on 1 line therapy was 2.83 higher for pts on TKI than for pts on chemotherapy in mt+ pts. With the advent of 2nd and 3rd generation TKI&inactives effective in 1st generation TKI resistant tumors, we wanted to study the impact of these drugs on the outcome of pts in a real life setting.

1360P Phase II trial of AZD9291 in second line treatment after acquired resistance with T790M mutation detected from circulating tumor DNA (LiquidOlung-O-Cohort 2)

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Background: Administering the best treatment after acquiring resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) requires the knowledge of the resistance status. In this trial, the treatment efficacy of osimertinib (AZD9291) was assessed in patients with non-small-cell lung carcinoma (NSCLC) harboring T790M resistance mutation, which was detected in the circulating tumor DNA (ctDNA) without re-biopsy of the tumor tissue.

Methods: To probe 60% response rate of osimertinib compared to 30% as null hypothesis, and considering 10% drop out rate, 19 subjects was recruited. To extract ctDNA, 15 ml of peripheral blood was withdrawn and centrifuged immediately before storage. Cobas v2 RUO (Roche diagnostics) and PANA mutyper™ (Pangenie, Korea) were used to detect the EGFR mutations from ctDNA. Osimertinib was prescribed as an 80mg tablet once in a day irrespective of the food intake.

Results: Eighty patients with acquired resistance to prior EGFR TKIs were screened for T790M resistance mutation, and the ctDNA of 21 subjects (26.3%) showed T790M mutation. T790M mutation was detected by both PANA mutyper™ and Cobas® in 13 cases, T790M was detected only by PANA mutyper™ in 4 cases, and only by Cobas® in 4 cases in 19 subjects. Nineteen subjects (age: 64.4 ± 11.7 years old, 14 women 5 men) were enrolled in this prospective single arm trial from September 2016 to April 2017. Prior EGFR TKIs were afatinib (n = 13), gefitinib (n = 4), gefitinib (n = 10), erlotinib and afatinib (n = 1), and gefitinib and afatinib (n = 1). Twelve subjects had exon 19 deletion of EGFR gene, 4 had L858R point mutation, one showed exon 19 deletion and L858R, 1 had G719S, and 1 case showed no activating mutation.

Conclusions: By April 2017, the response to osimertinib was evaluated in 13 subjects; 4 subjects dropped out from this trial before response evaluation, and the responses in 2 subjects are still pending for evaluation. Among the 13 subjects whose responses were evaluated (efficacy analysis set), partial remission was observed in 8 cases (61.5%). In the final efficacy analysis, toxicity and survival analyses will be performed.

Clinical trial identification: NCT02769286
Legal entity responsible for the study: Young-Chul Kim
Funding: AstraZeneca
Disclosure: Y.C. Kim: This study was funded by AstraZeneca. All other authors have declared no conflicts of interest.
Efficacy and safety of abemaciclib combined with either LY3023414 or pembrolizumab in stage IV NSCLC

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Background: Abemaciclib (abema), a cyclin D kinase 4-6 inhibitor, has single-agent activity and an acceptable safety profile when dosed continuously in patients with previously treated metastatic NSCLC (NCT01394016). In tumor models, CDK inhibition induces an escape pathway involving PI3K/AKT and abema induces synergetic immune activation with checkpoint inhibitors. We report on activity and safety of abema plus LY3023414 (LY), a PI3K/mTOR dual inhibitor, and abema plus pembrolizumab (pembro), an anti-PD-1 antibody, in an ongoing Phase Ib open-label, 3 + 3 multicenter trial of previously treated advanced NSCLC (NCT02079636).

Methods: For escalation, Abema (100, 150 mg, or 200 mg (cohort D) only) was given orally on a continuous schedule every 12 hours (q12h) with LY at 100, 150, or 200 mg q12h (cohort D) or with pembro at 200 mg IV. infusion q3 weeks (cohort E).

Confirmatory cohorts were given 150 mg abema with 150 mg q12h or 200 mg pembro. Pts were treated until progression or other discontinuation criteria were met. Responses were evaluated using RECIST v1.1. Safety assessments followed the NCI-CTCAE v4.0.

Results: As of 01-Mar-2017, cohort D (n = 29) had 62.1% males, 37.9% ≤65 years of age, median P prior systemic therapies = 3; 86.2% stage IV; 72.4% adenocarcinoma; 62.1% ECOG PS = 1; 9 pts (31%) had stable disease (SD); 3 pts had progressive disease (PD), and the status for the remaining 17 pts was unknown or under evaluation. There were 3 deaths unrelated to study drug (2 disease related and 1 stroke). 24/29 pts had a treatment emergent, related AE (TRA): 10/29 had a Grade 1-3 TRA. Any grade TRAEs (>30% pts) were nausea (51.7%), diarrhea (41.4%), and decreased appetite (31%). Cohort E had 19 pts entered (42.1% male, 42.1% <65 years of age, median P prior systemic therapies =2; 52.6% stage IV; 89.5% adenocarcinoma; 57.9% ECOG PS = 1). 8 pts (42.1%) had SD, 1 had PD, and the status for the remaining 10 pts was unknown or under evaluation. There were 3 disease related deaths. 15/19 pts had a TRAE: 5/15 had a G3/4 TRAE. Any grade TRAEs (>30% pts) were fatigue (n = 47.4%) and diabetes (36.8%).

Conclusions: To date, stable disease as best response and acceptable safety have been observed using combinations of abema and either LY or pembro in advanced NSCLC.

Clinical trial identification: NCT02079636

Legal entity responsible for the study: Eli Lilly and Company

Funding: Eli Lilly and Company

Disclosure: P. Garrido Lopez: Advisor/Board member: MSD, Pfizer, BMS, Novartis, Roche, Bl, Guardiant Speakers Bureau: MSD, Pfizer, BMS, Novartis, Roche

Honorary recipient: Bl J. Goldman: Research grant from Eli Lilly and company Eli Lilly and Company’s Scientific Advisory Board member. K. Kelly: Attended a Lilly ad-

Honorarium recipient: BI J. Goldman: Research grant from Eli Lilly and company Eli Roche, BI, Guardant Speakers Bureau: MSD, Pfizer, BMS, Novartis, Roche

P. Garrido Lopez: Advisor/Board member: MSD, Pfizer, BMS, Novartis, Eli Lilly and Company

References:

Conclusions: Final clinical results from SUNRISE: A phase III, randomized, double-blind, placebo-controlled multicenter trial of bavituximab plus docetaxel in patients with previously treated stage IIIb/IV nonsquamous non-small cell lung cancer


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Background: Exposed phosphatidylinerse (PS) in the tumor microenvironmen is highly immunosuppressive. Bavituximab targets PS and repolarizes M2 macrophages to M1 resulting in production of pro-inflammatory cytokines such as IFN-γ and IL-12, maturation of dendritic cells, and tumor specific cytotoxic T lymphocyte immunity. In a prior blinded Phase II trial in 2nd-line nonsquamous NSCLC, bavituximab + docetaxel was well-tolerated and demonstrated 60% improvement (11.7 vs 7.3 months) in median overall survival (mOS) (HR, 0.66; P = 0.11) compared to control.

Methods: 597 patients with Stage IIIb/IV nonsquamous NSCLC that progressed on platinum-double chemotherapy were randomized 1:1 to receive up to six 21-day cycles of docetaxel in combination with weekly 5 mg/kg bavituximab (B + D) or placebo (D) until progression or toxicity. The primary endpoint was OS. Secondary endpoints included progression-free survival (PFS), objective response rate (ORR) and safety.

Results: With 12 months follow-up from the last patient randomized and >85% of the targeted OS events reached, mOS was 10.5 months (95% confidence interval [CI], 8.4-11.9) among 297 patients in B + D and 10.9 months (95% CI, 9.2-12.1) among 300 patients in D (HR, 1.06; P = 0.534). PFS was 4.2 months (95% CI, 3.9-4.6) in B + D and 4.1 months (95% CI, 3.2-4.8) in D (HR, 1.02; P = 0.876). The ORR was 15% in B + D vs. 11% in D (odds ratio, 0.7; P = 0.15). The safety profile was similar between groups. Grade 3 or higher adverse events occurred in 68% of patients in B + D and 60% in D. In an unplanned analysis of OS for patients who received subsequent immune checkpoint inhibitors (ICI), the mOS was not reached (95% CI, 15.2-NA) in B + D (n = 46) and 12.6 months (95% CI, 10.4-17.8) in D (n = 47) (HR, 0.46; P = 0.006).

Conclusions: The combination of B + D was well-tolerated though no OS difference was observed compared to D alone in the ITT population of previously treated nonsquamous NSCLC. An exploratory analysis of patients who received subsequent ICI found significantly longer OS in patients who received prior B + D than those who received D and support further clinical investigation of B + ICI in NSCLC.

Clinical trial identification: NII = NCT01999673 EudraCT = 2013-003953-13

Legal entity responsible for the study: Peregrine Pharmaceuticals Inc.

Funding: Peregrine Pharmaceuticals Inc.

Disclosure: P. Bidoli: Eli Lilly personal fees and advisory board BMS personal fees and advisory board Boehringer personal fees and advisory board. M. Rock: Honoraria for lectures and consultancy with Hoffmann-La Roche, Lilly, MSD, Merck, BMS, AstraZeneca, Celgene, Boehringer-Ingelheim, Pfizer, Novartis. N. Kallinteris, J. Lai: Peregrine Pharmaceuticals Inc. — employee, stock ownership M. Tang: Peregrine Inc. Employee, stock owner. J. Shan: Employee, officer and stock owner for Peregrine Pharmaceuticals Inc. All other authors have declared no conflicts of interest.
Effect of quality of life (QoL) of patients with squamous (SCC) non-small cell lung cancer (NSCLC) (ABOUND.sqm)


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Background: Patients with advanced NSCLC experience a high symptom burden, therefore, identifying a treatment that maintains or improves QoL is important. QoL outcomes in patients with SCC NSCLC receiving nab-P/C induction in the induction part of the ABOUND.sqm study are reported.

Methods: Patients with stage IIIIB/IV SCC NSCLC and no prior chemotherapy for metastatic disease received 4 cycles of induction therapy with nab-P 100 mg/m² days 1, 8, 15 and 22 cycles + 5-C auro under the curve 6 on day 1 (21-day cycles). Patients not progressing after induction received (2:1) maintenance nab-P 100 mg/m² days 1 and 8 (21-day cycles) + best supportive care (BSC) or BSC alone until progression/unacceptable toxicity. The primary endpoint is progression-free survival (randomization to maintenance).

Patient-reported QoL (exploratory endpoint) was assessed on day 1 of each cycle using the Lung Cancer Symptom Scale (LCSS) and EuroQol 5 Dimensions -5 Levels (EQ-5D-5L).

Results: In 343 patients receiving treatment in the induction phase were evaluated. Median age was 68 years, 90% were white, 68% male, and 67% had ECOG PS 1. Of 532 patients treated for ≥ 2 cycles, 298 (90%) completed baseline ≥ 1 postbaseline QoL assessment. During induction, the mean change from baseline in LCSS symptom burden index and total score ranged from 5.5%-7.8% and 5.5%-7.7%, respectively. Clinically meaningful improvements (≥ 10 mm [visual analog scale]) from baseline were observed in composite LCSS pulmonary symptom items of cough, shortness of breath, and hemoptysis in 44% of patients. Each individual dimension of the EQ-5D-5L was maintained/improved from baseline in the majority of patients (82%-91%), and ≥ 32% reported complete resolution at least once during treatment.

Conclusions: QoL was improved/maintained in patients with advanced SCC NSCLC treated with nab-P/C induction therapy. These results continue to support nab-P/C as a treatment option in patients with SCC NSCLC, as was initially demonstrated in a subset analysis of the phase III registration trial. NCT020724728.

Clinical trial identification: NCT020724728

Legal entity responsible for the study: Celgene Corporation

Funding: Celgene Corporation

Disclosure: V. Villafiori: Research funding from Celgene and Novartis paid directly to University of Chicago. J. Knoble: Consulting or advisory role for Cardinal Health, Speakers’ bureau for Novartis, Alexion and Celgene. M. Thomas: Received honoraria for an advisory/speaker role from: Celgene, AstraZeneca, Roche, BMS, Lilly, Novartis, Boehringer. P. Staib: Honoria, consulting or advisory role, speaker’s bureau and research funding: Celgene. T. Chen, N. Trunova: Employment and Stock Ownership: Celgene. D.R. Spigel: Research funding, consulting or advisory role, and travel, accommodations, expenses: Celgene. All other authors have declared no conflicts of interest.

Quality of life (QoL) in elderly NSCLC patients (pts) treated with nab-paclitaxel/carboplatin (nab-P/C) in the ABOUND.70+ trial


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Background: Treatment of elderly pts with advanced NSCLC remains challenging, and the impact of therapies on QoL can be an important factor in clinical decisions. nab-P/C demonstrated efficacy in a subset of pts ≥ 70 yrs with NSCLC in a phase 3 trial.

484 | NSCLC, metastatic
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ABOUND 7.0+ was designed to determine whether a 1-wk break can further improve tolerability of nab-P/C in these patients. QoL outcomes are reported here.

Methods: Pts ≥ 70 yrs with locally advanced/metastatic NSCLC were randomized 1:1 to first-line nab-P 100 mg/m² on d 1, 8, and 15 + C AUC 6.0 on d 1 of a 21-day cycle (Arm A) or the same regimen with a 1-wk break between cycles (Arm B). Primary endpoint: percentage of pts with grade ≥ 2 peripheral neuropathy or grade ≥ 3 myelo-suppression. Key secondary endpoints: PFS, ORR, OS for which statistical analyses do not control for type I error (P values unadjusted). QoL (exploratory endpoint) was assessed using Lung Cancer Symptom Scale (LCSS) and EuroQol-5 Dimensions-5 Levels (EQ-SD-SL) at d 1 of each cycle.

Results: At interim evaluation, primary endpoint was similar across arms, resulting in early closure of enrollment. In Arms A and B, 78% and 79% completed a baseline and ≥2 postbaseline QoL assessment. LCSS item of cough improved with each cycle; at the end of cycle 6, mean change from baseline in Arms A and B was 25.4 and 13.8 mm (visual analog scale). For cough, median time to deterioration (TTD) was 4.4 and 4.7 mos (P = 0.7093). For the composite LCSS pulmonary symptom items of cough, shortness of breath, and hemoptysis, the median TTD was 4.4 and 6.0 mos (P = 0.3347). Mean maximum improvement (at any point during treatment) in EQ-SD-SL visual analog scale was 10.1 and 12.8 points. Table lists key safety, efficacy and QoL data.

Table: 1367P

<table>
<thead>
<tr>
<th>Safety</th>
<th>Arm A n = 71</th>
<th>Arm B n = 72</th>
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<tbody>
<tr>
<td>Primary endpoint, n (%)</td>
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<td></td>
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<tr>
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<tr>
<td>Grade ≥ 2 peripheral neuropathy</td>
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<td>54/70 (77)</td>
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<tr>
<td>Grade ≥ 3 myelosuppression</td>
<td>25/68 (37)</td>
<td>25/70 (36)</td>
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<td>Anemia</td>
<td>39/68 (57)</td>
<td>39/70 (56)</td>
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<tr>
<td>Thrombocytopenia</td>
<td>14/68 (21)</td>
<td>17/70 (24)</td>
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<tr>
<td>Mean maximum improvement from baseline, mm</td>
<td></td>
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<tr>
<td>LCSS Total score</td>
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<td>11.7</td>
</tr>
<tr>
<td>LCSS Pulmonary symptom</td>
<td>9.2</td>
<td>14.9</td>
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</table>

Conclusions: These results support nab-P/C as a treatment option in elderly pts with NSCLC. Safety (primary endpoint) and OS were similar across the two arms, while there was a signal of improvement in ORR, PFS, and QoL with a 1-wk break. NCT02131149

Clinical trial identification: NCT02131149

Legal entity responsible for the study: Celgene Corporation

Funding: Celgene Corporation


Background: Although nab-PTX plus carboplatin is one of the standard treatment for chemo-naive non-small cell lung cancer (NSCLC), the efficacy, safety and optimal schedule of nab-PTX monotherapy as 2nd or 3rd line for NSCLC pts without any driver mutations remains unknown.

Methods: This was a single arm phase I/II study. Eligible pts are advanced NSCLC without EGR mutation and ALK rearrangement that progressed after platinum-doublet chemotherapy. The pts were received 100 mg/m² of nab-PTX on day 1, 8, 15 and 22 (level 0) on day 1, 8 and 15 (level 1) every 4-week in phase I. Dose limiting toxicities (DLT) were assessed and the recommended schedule was determined in the phase I. The primary endpoint is objective response rate (ORR), assuming that estimated ORR was 15% and threshold ORR was 5% with error of 0.05 and 0.2 in the phase II part. Total 55 pts were planned to be enrolled.

Results: The recommended schedule of nab-PTX was determined as the level -1, because the DLTs were found in 4 of 5 pts in level 0. Total 55 pts were enrolled in the phase II and the characteristics were as followings; median age, 66 years (range, 41–90 years), male/female = 40/15, PS 0/1/2 = 12/39/4, 2nd/3rd line = 34/21, adeno/squamous/ large/others = 34/17/2. The median number of treatment cycles was three (range, 1–10). The ORR was 7.9% (95% CI, 2.0–17.6%); (PR (n = 4), SD (n = 26), PD (n = 24), and NE (n = 1)). At the median follow-up time of 5.3 months (range, 1.9 – 26.0 months) for all pts, the median PFS was 3.4 months (95% CI, 1.9 – 4.0 months), Treatment related grade 3 or 4 toxicities were neutropenia (36%), pulmonary infection (3.6%), and pneumonitis (5.4%). One patient (2%) was died due to treatment-related ARDS.

Conclusions: In phase I part, we confirmed that schedule level -1 was tolerable and the schedule had been recommended. In phase II part, this study failed to meet predefined primary endpoint although PFS was comparable and toxicity was acceptable for pts with advanced NSCLC without any driver mutations as 2nd or 3rd line treatment. Clinical trial identification: UMN00012404.

Legal entity responsible for the study: Okayama Lung Cancer Study Group

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Results: A total of 334 pts were included in this analysis. Median age was 68 yrs; 90% were white, 68% male, and 68% had ECOG PS 1. During induction, 145/334 pts (43%) discontinued treatment. Of these, 31/145 (21%) due to adverse events, 16/145 (11%) each due to death and pt withdrawal, 13/145 (9%) due to symptomatic deterioration, 9/145 (6%) due to other, and 1/145 (<1%) due to protocol violation. The median percentage of per-protocol dose of nab-P was 74%; median nab-P dose intensity and cumulative dose were 74.08 mg/m²/week and 80.9 mg/m², respectively. nab-P dose modifications included ≥1 reduction, missed dose, or dose delay in 55%, 60%, and 60% of pts, respectively. Grade ≥3 TEAEs were mainly hematologic and included neutropenia (48/334 [14%]), anemia (92/334 [38%]), and thrombocytopenia (48/334 [14%]). Grade ≥3 peripheral neuropathy was observed in 14/334 pts (4%).

Conclusions: This interim analysis demonstrates the safety and tolerability of nab-PCS induction therapy in pts with SCC.

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1371P Diagnostic and therapeutic strategies for elderly patients with advanced non-small cell lung cancer (NSCLC): Results from an EORTC pan-European survey

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Background: The EORTC Lung Cancer Group (LCG) and the Elderly Task Force (ETF) developed a pan-european survey that aims to provide an overview of the management and treatment strategies for elderly patients (pts) diagnosed with advanced NSCLC, as well as to identify potential needs and scientific pending questions that could be addressed in new trials.

Methods: An electronic 13-topic survey explaining the study purpose was developed and sent to all EORTC LCG and ETF members. The 25-items included multiple-choice and open-ended questions requesting the following information on geodemographics (6 items), pt population (3 items) and diagnostic, treatment preferences and outcome (4 items). Elderly pts were defined as those older than 70 years.

Results: Sixty-two individual sites, from 19 countries, completed the online questionnaire. In 42 centers (67.9%) there is no dedicated team for the management of advanced non-small cell lung cancer (NSCLC) for elderly pts; on the other hand, only in 2 centers (3.2%) pts with suspected NSCLC are not discussed by a multidisciplinary board. Notably, oncogeriatric assessment is routinely performed in 17 (27.4%) centers; 93% of the scales are both the preferred evaluation tools (53.5%, 23.6% and 11.6% respectively). In 58% of the preferred first-line chemotherapy regimens are Carboplatin (CBDA)-Pemetrexed (PEM) (19 (31.7%), CBDA-Paclitaxel (PAC) (15 (24.2%), Carboplatin (CBP)-PEM (14 (22.6%), CBDA-Gemcitabine (GEM) (10 (15.5%), other (3 (4.8%)). In the second line setting the preferred treatments are Nab-Pumab 30 (45.5%), PEM 11 (16.7%), Docetaxel 9 (13.6%), PAC8 (12.1%), GEM 4 (6.1%), Erlotinib 4 (6.1%), while PEM 13 (24.2%), Nab-Pumab 13 (20.1%), PAC9 (15.4%), Docetaxel 6 (9.2%), GEM 6 (9.7%), other 11 (17.7%) represent a seconded option.

Conclusions: The survey provides an overview of the clinical practice in the management of elderly patients with advanced NSCLC, summarizing relevant and updated background for the possible development of future collaborative trials. In this survey, different treatment regimens are used by different centers, and geriatric assessment is used heterogeneously, reflecting the lack of a "standardized" approach and the need for further research in this area.

Legal entity responsible for the study: EORTC

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1372P Diversity of brain metastasis (BM) management in non-small cell lung cancer (NSCLC) in Europe (EU): Results of the Young Investigators European Organisation for Research and Treatment of Cancer Lung Cancer Group (YI EORTC LCG) survey

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Background: BM are frequent in NSCLC patients (pts) but management can vary. Methods: An online survey containing questions on NSCLC BM screening and treatment (tx) was widely distributed between 16/02/17 and 16/04/17 to all EORTC LCG members, and through several EU societies involved in lung cancer tx.

Results: 478 physicians (phys) (radiation oncologist: 51.9%, pulmonologist: 27%, medical oncologist: 15.3%, others: 5.8%, 73.2% with >5 years experience in NSCLC) responded. Italy (17.8%), Netherlands (14.2%), UK (13.0%), and France (11.5%) contributed most. 84.9% screened neurologically asymptomatic pts for BM at diagnosis (49% used MRI). Pts screened stage III (66.9%) and IV (40.8%) most often. 35.4%
used a prognostic (p) classification to guide initial tx decisions. In 48.1% lowest p-score threshold to actively treat pts did not differ between driver mutation (MUT +) and non-driver (MUT -) pts. 38.1% used less WBRBT in poor prognostic pts based on QUARTZ trial (NCT8230061) results. 88% had access to stereotactic radiosurgery (SRS). After single BM surgery, 50.8% systematically prescribed adjuvant SRS or WBRT, and 44.2% only in case of incomplete resection. Preferred tx in neurologically asymptomatic pts-naive pts diagnosed with ≥ 3 BM was systemic tx (78.4%). 46% stated that WBRT could increase systemic tx efficacy. 44.8% stated that all pts with tyrosine kinase inhibitors (TKI) and immune checkpoint blockers (IO) were discontinued (timing varied) during SRS/WBRT, respectively. Drugs that were most often continued during SRS/WBRT were erlotinib (44.5-40%), gefitinib (38.0-34.4%), afatinib (29.9-25.1%), crizotinib (32.2-27.6%) and IO (PD-1): 1-28.4-22.8%, CTLAA: 10-9.8%, because of perceived safety issues (44.6%) or risk of systemic failure (37.9%). MUT + pts with ≥ 3 BM were more likely to receive SRS than MUT −. 76% of pts preferred local tx & TKI continuation over a switch to next-line tx in pts with only intracranial progression.

Conclusions: BM management differs: screening is not uniform, p-classifications are not often used, and MUT + NSCLC pts generally receive more aggressive local tx.

Legal entity responsible for the study: SORCT Lung Cancer Group

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1373P Clinical features of never smoker patients with lung squamous carcinoma: A retrospective multicenter study

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Background: Squamous cell carcinoma of the lung (LSCC) is the second most common histological subtype of non-small cell lung cancer (NSCLC) having smoking habit as the major risk factor. LSCC in non-smokers is an exceptional finding possibly related to professional exposure and subsequent carcinogenesis even though clinical and biological landscape is largely unexplored.

Methods: This is a retrospective multicenter study investigating clinical features of never-smoker LSCC patients (pts) referred to three Italian Centers between 2010 and 2016. Relapse (RFS) or progression free (PFS) and overall (OS) survival curves were calculated by Kaplan-Meier method. Cox regression proportional hazards model was used to estimate the impact of covariates on OS.

Results: Among 791 LSCC pts, 37% (46%) occurred in never-smokers; our case series included 19 males and 18 females with a median age of 63 years. ECOG PS was 0-1 in 60% of pts. The majority of pts had ECOG PS <2 (50%), breast (31%), and respiratory disease (24%). In all patients, ineligibility was identified as an end point of trial; more patients were female (58%), and 50% were younger than 50 years. Of 786 patients, 469 (60%) were ineligible for clinical trials. The main reasons for ineligibility were brain metastasis (41%), a poor performance status (PS) (35%), and respiratory disease (24%). In all patients, ineligibility was identified as an independent predictor of overall survival (OS) (adjusted hazard ratio [HR] 0.78, 95% confidence interval [CI], 0.65–0.93, P = 0.008), even in patients with a good PS who received chemotherapy (HR 0.80, 95% CI, 0.65–0.99, P = 0.037). In subgroup analyses of ineligible patients, the survival varied depending on the reasons for their ineligibility. In particular, prior cancer history was not associated with a poor outcome, though this was a common reason for ineligibility (14%).

Conclusions: Most patients were ineligible for clinical trials and had shorter survival. The survival of ineligible patients varied depending on the reasons for their ineligibility. We should consider these results when applying clinical trial outcomes to real-world patients. More studies for ineligible patients are needed to improve real-world treatment.

Legal entity responsible for the study: Daichi Fujimoto

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1375P Treatment paradigm shift in NSCLC: Patient data analysis from 2005 to 2016

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Background: In the last decade, chemotherapy were the SoC in advanced NSCLC treatment with limited benefit to long-term survival. Discovery of EGFR/ALK and PD1/PDL1 follow by approval targeted therapies (TTs) and immunotherapies (IOM), respectively, marked two major treatment shifts. In addition, scientific advancement on drug resistance issued from TTs and new drug gable mutations continue to transform the treatment landscape and options for patients with advanced NSCLC.

Methods: This study used IMS Oncology AnalyzerTM a syndicated, retrospective, longitudinal cancer treatment database collecting anonymized patient-level oncology data in EUS, projected to national level. Data collected between 2005 and 2016 was used to identify changes in the treatment paradigm in advanced NSCLC. Three time period groups have been compared: period 1: from 2005 to 2008, period 2: from 2009 to 2014 and period 3: 2015 and 2016.

Results: Of the currently 1,602,026 (projected number) treated populations, there is an increase in protein kinase Inhibitors (TKIs) usage, mainly represented by anti EGFR and anti ALK, from 8% to 23% to 30% in period 1, 2 and period 3 respectively. Monoclonal antibodies (MAB) follows a similar trend increasing from 1% to 15% in the last years, respectively, while the platinum agents slightly decreases. IOs captures 52% in the last couple of years from the overall MAB group. Till recently, bevacizumab (BEV) was leading this therapeutic class. Increased granularity in patient stratification, will allow identification of more spectacular treatment changes or identification of those who would have passed unnoticed. In IL, mutant segment, paradigm switch occurred end 2008 when TKIs reached directly 84%. In 2L, IOs jump is much less noticeable, entering directly in the last analyzed period with 25% from MAB group. In WT segment, we can notice 2 switches 2015/2016 period, where BEVA reached dire- cly 13% and a second one in 2L end 2016, when MABS captured 28%, with IOs repre- senting 9% from this therapeutic group. Conclusions: Currently, the advent of IOs has completely overshadowed existing TTs. Emerging genetic markers (ROS-1, KRAS, RET), specific EGFR/ALK mutations due to resistance along with combinations of IOs and TTs will continue to add new treatment outcomes of such ineligible patients. Therefore, we investigated the characteristics, outcomes, and survival of advanced NSCLC patients who were ineligible for clinical trials.

Methods: We analyzed a retrospective cohort of 786 consecutive patients diagnosed with advanced NSCLC between January 2006 and December 2014. We reviewed the criteria in phase 3 clinical trials, and classified patients using the common first-line eligibility criteria for lung cancer.

Results: Of the 786 patients, 469 (60%) were ineligible for clinical trials. The main reasons for ineligibility were brain metastasis (41%), a poor performance status (PS) (35%), and respiratory disease (24%). In all patients, ineligibility was identified as an independent predictor of overall survival (OS) (adjusted hazard ratio [HR] 0.78, 95% confidence interval [CI], 0.65–0.93, P = 0.008), even in patients with a good PS who received chemotherapy (HR 0.80, 95% CI, 0.65–0.99, P = 0.037). In subgroup analyses of ineligible patients, the survival varied depending on the reasons for their ineligibility. In particular, prior cancer history was not associated with a poor outcome, though this was a common reason for ineligibility (14%).

Conclusions: Most patients were ineligible for clinical trials and had shorter survival. The survival of ineligible patients varied depending on the reasons for their ineligibility. We should consider these results when applying clinical trial outcomes to real-world patients. More studies for ineligible patients are needed to improve real-world treatment.

Legal entity responsible for the study: Daichi Fujimoto

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1376TP Phase III study of atezolizumab (atezo) vs chemotherapy (chemo) in patients (pts) with treatment-naive advanced, recurrent or metastatic NSCLC unsuitable for platinum (plat)-based chemo

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Background: Most pts with newly diagnosed NSCLC have locally advanced or metastatic disease, with 30%-40% having poor performance status (ECOG PS ≥ 2) due to...
disease burden and comorbidities. These pts have poor prognosis vs pts with PS < 2 and higher toxicity with standard doublet chemotherapy. Despite limited efficacy, single-agent chemo (vinorelbine [vin], gemcitabine [gem], docetaxel [doc]) is often used for pts who do not tolerate Concurrent or platinum-based regimens, highlighting the need for new treatments. Atezo (anti–PD-L1) prevents PD-L1 from binding to its receptors PD-1 and B7.1, restoring cancer-specific T-cell immunity. In OAK, a Phase III 2L+ NSCLC study, atezo monotherapy was well tolerated and showed significant OS improvement vs doc for advanced disease, and no EGRF/ALK mutation/ALK translocation. Approximately 1,199 pts will be randomized to 1 of 3 arms: A (avelumab 10 mg/kg q1 week IV QW), arm B (investigator’s choice of specified platinum-based chemotherapy), or arm C (avelumab 10 mg/kg every week for 12 weeks, then 10 mg/kg Q2W), stratified by NSCLC histology and baseline tumor PD-L1 expression level. Secondary endpoints include objective response, duration of response, safety, pt-reported outcomes, PK, and biomarker assessments.

Clinical trial identification: NCT02576740 Protocol number: EMR 100070-005

Legal entity responsible for the study: Pfizer Inc., New York, NY, USA and Merck KGaA, Darmstadt, Germany.

Funding: Pfizer Inc., New York, NY, USA and Merck KGaA, Darmstadt, Germany.


492 | NSCLC, metastatic

41777TP JAVELIN Lung 100: updated design of a phase 3 trial of avelumab vs platinum doublet chemotherapy as first-line (1L) treatment for metastatic or recurrent PD-L1 + non-small-cell lung cancer (NSCLC)


Background: Avelumab is a human anti–PD-L1 IgG1 antibody that has shown promising antitumor activity and manageable tolerability across multiple tumor types, including NSCLC. The PEARL study aims to assess first-line PD-L1 expression: PEARL

Y.-C. Wu1, S. Lu2, S. Clarke1, K. Lactionov4, P. L. Kirkby4, M. Kirkby4, Y. Xie6, P. Stockman7

Clinical trial identification: NCT03003962

A phase 3 study of first-line durvalumab vs platinum-based chemotherapy in patients with advanced NSCLC and high PD-L1 expression: PEARL

Y.-C. Wu1, S. Lu2, S. Clarke1, K. Lactionov4, P. L. Kirkby4, M. Kirkby4, Y. Xie6, P. Stockman7

A randomized, open-label comparison of lorlatinib versus crizotinib as first-line treatment for advanced anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer

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Background: Lorlatinib and crizotinib are oral tyrosine kinase inhibitors with activity against ALK and ROS1 fusion proteins. Crizotinib is well tolerated and has superior efficacy compared to chemotherapy for treatment of patients (pts) with advanced ALK+ NSCLC. However, resistance to crizotinib can develop, and the central nervous system (CNS) is often a site of disease relapse. Lorlatinib is a CNS penetrant and has potent activity against de novo fusions and kinase domain resistance mutations. Lorlatinib has shown clinical activity in pts previously treated with crizotinib and other ALK inhibitors, including pts with progressive CNS metastases. This study aimed to determine if lorlatinib is superior to crizotinib in prolonging progression-free survival (PFS) in treatment-naïve pts with advanced ALK+ NSCLC and to identify candidate biomarkers predictive of clinical efficacy or treatment resistance.

Trial design: This global, multicenter, open-label phase 3 study will enroll ~280 treatment-naïve pts. Eligible pts must be aged ≥18 years, have Eastern Cooperative Oncology Group performance status of 0–2 and ≥1 measurable extracranial target lesion not previously treated with radiotherapy. Pts with asymptomatic brain metastases are eligible. Pts will be randomized (1:1) to lorlatinib 100 mg once daily or crizotinib 250 mg twice daily and stratified by presence of brain metastases (yes/no) and ethnicity (Asian/non-Asian). Treatment will continue until disease progression, pt refusal, or unacceptable toxicity. Crossover between treatment arms will not be permitted. The primary endpoint is PFS based on blinded independent central review (BICR) using RECIST v1.1. Secondary endpoints include PFS based on investigator assessment (IA), overall survival, objective response (OR) by BICR and IA, intracranial (IC) OR, IC time to progression, duration of response, time to response by BICR, tumor tissue and peripheral blood circulating free DNA biomarker assessment, safety, and pt-reported health-related outcomes. The first pt was screened on April 14, 2017. This study is registered with ClinicalTrials.gov as NCT03052608.

Clinical trial identification: NCT03052608

Legal entity responsible for the study: Pfizer

Funding: Pfizer

Disclosure: A.T. Shaw: Membership of an advisory board or board of directors - Blueprint medicines, KSC therapeutics. Honoraria or Consulting - Pfizer, Novartis, Ariad, Genentech/Roche, Ignyta, Daiichi-sankyo, Taiho, LOXXO, Blueprint medicines, EMD Serono, Foundation Medicine. T. Takahashi: Corporate sponsored research - AstraZeneca, Pfizer, Eli Lilly, Chugai Pharmaceutical Co, Ono Pharmaceutical Other, please specify; Honoraria - Astra Zeneca, Pfizer, Eli Lilly, Chugai Pharmaceutical, Ono Pharmaceutical. C.S. Baik: University of Washington: Pfizer; Novartis, Loxo Oncology, Genentech, MedImmune, Mirati Therapeutics, Clovis Oncology, GlaxoSmithKline, Eisai, Colgene, Bristol-Myers Squibb, Merck Sharp & Dohme Corp, Clovis Oncology and Novartis. A. Polli: Stock ownership - Pfizer. M. Carpentieri: Stock ownership - Pfizer Other relationships (such as employment) with a pharmaceutical company - Pfizer. J.F. Martini: Stock ownership - Pfizer Other relationships (such as employment) with a pharmaceutical company - Employee (Pfizer). B.J. Solomon: Membership of an advisory board or board of directors - Advisory Boards: Pfizer, Novartis, Roche-Genentech, AstraZeneca, Merck, Bristol Myers Squibb. All other authors have declared no conflicts of interest.
Background: Poly (ADP-ribose) polymerase inhibitors (PARPi) have demonstrated impressive efficacy in BRCA-mutated gynaecological malignancies. Several lines of evidence raise concerns that the DNA repair (DDR)-deficient populations that benefit from PARPi go far beyond BRCA-deficiency. Non-small cell lung cancer (NSCLC), the first evidence now support that the DNA repair (DDR)-deficient populations that benefit from PARPi. Maintenance PARPi could therefore benefit to patients (pts) with platinum-sensitive NSCLC. Olaparib (Lynparza), a potent and selective PARPi, was the first-in-class approved PARPi in BRCA-mutated ovarian cancer.

Trial design: PIPSeN is a randomized double-blind phase II investigator-initiated study evaluating maintenance Olaparib versus placebo in pts with platinum-sensitive advanced NSCLC. Chemosensitive EOCOG PS 0-1 pts with stage III-IV NSCLC with no EGR mutation or ALK translocation are eligible. Treatment consists of an “induction phase” of 4-6 cycles platinum-based therapy (any doublet), followed by a “randomized phase” where pts receiving partial or complete response are randomized between Olaparib maintenance (tablets, 300mg bd) and placebo until progression or unacceptable toxicity. Primary objective is to assess the efficacy of maintenance Olaparib as measured by Progression-Free Survival from randomisation (RECIST v1.1). Secondary objectives include comparison of overall survival, disease control rate and safety. Randomisation is stratified according to age, histology and country. With an anticipated HR for the primary endpoint of 0.65 (bilateral a = 0.2; b = 0.2), approximately 950 enrolled pts will be required to randomize 144 pts and observe 97 events. T: 0.05.

Funding: Boehringer Ingelheim. K.M. Kerr: Personal fees from Boehringer-Ingelheim, Hoffmann-La Roche, Lilly, MSD, BMS, AstraZeneca, Celgene, Merck and Pfizer. N. Morlik, K. Pietzko, T. Kitzing, J. Braunger: Author is an employee of Boehringer-Ingelheim. K.M. Kerr: Personal fees from Boehringer Ingelheim, during the conduct of the study. All other authors have declared no conflicts of interest.

Clinical trial identification: EudraCT: 2014-005586-75 NCT02679963

Legal entity responsible for the study: Gustave Roussy Cancer Campus (sponsor), in collaboration with the Spanish Lung Cancer Group

Funding: AstraZeneca

Disclosure: D. Planchard: Consultancy fees for AstraZeneca, Boehringer Ingelheim, BMS, Lilly, MSD, Pfizer, Roche, Novartis, Chugai, Majidi: Merk Sharp and Dohme, Boehringer Ingelheim, Bristol-Myers Squibb, Roche, Novartis honoraria. F. Barlesi: AstraZeneca Honoraria. S. Viteri: Consulting/advisory (BI, Clovis, Idoa Pharma, Novartis, Roche, Taropen) Research (AbbVie, ARIAD, Astra, AstraZeneca/MedImmune, BI, Clovis, CyxThera, Daichi Sankyo, GSK, Ham, Incyte, Merck, Novartis, Pfizer, Puma, Roche, Servier, Yamen). B. Besse: Research grants from AstraZeneca. J. C. Soria: Consultancy fees from AZ. All other authors have declared no conflicts of interest.

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Background: Several clinical trials have confirmed the safety and efficacy of aterozilium (atero–anti-PD-L1) monotherapy in advanced NSCLC, including in PD-L1–selected IL patients (pts). Independent of PD-L1 status, high TMB is associated with aterozilium efficacy. Alectinib is a potent, selective ALK/RET kinase inhibitor currently approved for NSCLC pts previously treated with crizotinib and is expected to have activity in 1L advanced or metastatic NSCLC.

Trial design: B-FIRST (NCT02671422) is an ongoing, prospective, European, multicentre, non-interventional study (N=100) investigating whether biomarkers (germline or somatic mutations) can predict OS in adults with advanced adenocarcinoma NSCLC initiating nintedanib + docetaxel according to the nintedanib label. Tissue/serum samples will be collected in the first-line therapy will be used for biomarker analyses. To ensure sample quality and tumour content across all slides, the first, middle and last slides will be haematoxylin/cosin-stained and assessed by a certified pathologist for tumour content, extent of necrosis and immune cell infiltration. Tissue DNA and RNA will be co-isolated from unstained slides (AllPrep DNA/RNA FFPE Kit) and quantitated with QicGreen and Ribogreen reagents, respectively. Tissue DNA sequencing libraries will be prepared using a capture-based targeted gene panel covering whole exome of NSCLC-related genes (e.g. EGFR, KRAS, ALK, BRAF, PIK3CA, TP53) and qubitadn target genes (VEGFR1–3, FGFR1–3, PDGFBR n/ b) and analysed by Illumina next-generation sequencing (NGS). Transcriptomics analyses will be conducted to (1) complement DNA analyses by providing further information on gene fusions; and (2) enable tumour classification into transcriptional subtypes. Tissue RNA libraries will be prepared and analysed by NGS or, if RNA quantity/quality is insufficient for sequencing, digital gene expression analysis (nCounter Gene Expression Panels) will be performed. Unstained slides will also be analysed by immunohistochemistry for immun- and proliferation-related protein expression (PD-L1, ki-67). The primary endpoint is OS, which will be analysed according to biomarker status.

Clinical trial identification: NCT02671422

Legal entity responsible for the study: Boehringer Ingelheim Pharma GmbH & Co. KG

Funding: Boehringer Ingelheim Pharma GmbH & Co. KG

Disclosure: M. Reck: Author reports personal fees from Boehringer-Ingelheim, Hoffmann-La Roche, Lilly, MSD, BMS, AstraZeneca, Celgene, Merck and Pfizer. N. Morlik, K. Pietzko, T. Kitzing, J. Braunger: Author is an employee of Boehringer-Ingelheim. K.M. Kerr: Personal fees from Boehringer Ingelheim, during the conduct of the study. All other authors have declared no conflicts of interest.
Clinical trial identification: NCT02848651, B-FAST NCT number available on poster
Legal entity responsible for the study: F. Hoffmann-La Roche Ltd.
Funding: F. Hoffmann-La Roche Ltd.
Disclosure: T.S.K. Moh: Stp. AZ, BI, PFE, NV, SFI, ROG, MSD, CLVS, BMS, Eisai, Taiho ROG/GNE, LLY, NV; Stock Sanomastics AB: AZ, ROG/GNE, PFE, LLY, BI, CLYS, MSD, NV, SFI, ACEA Bio, VRTX, BMS, GeneDecode, ODX, CELG, RXDX; R, Boehringer Ingelheim, Eli Lilly, Pfizer, Bristol Myers- Squibb and Genentech/Roche. E. Schleifman: Consulting or advisory role: AstraZeneca, Celgene, BI, Eli Lilly, N. Karachaliou: Employee: Genentech; S. Mocci: Employee: Boehringer, Clovis, Daiichi Sankyo, GSK, Hanmi, Incyte, Merck, Novartis, Pfizer, Puma, Roche, Servier, Vaxom. Advisor: Boehringer, Clovis, Idera Pharma, Novartis, Promega Biotech, Roche, Targovax. E. Felip Font: Personal fees (Consulting fees) from: Boehringer Ingelheim, Eli Lilly, Pfizer, Roche and MSD, Astra Zeneca and Bristol Myers Squibb. All other authors have declared no conflicts of interest.

### Table: 1383TIP B-F1RST and BFAST Study Details

<table>
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<th>Study</th>
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<th>Key Secondary Endpoints</th>
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<tr>
<td><strong>B-F1RST Phase II</strong></td>
<td>Atezo 1200 mg IV q3w</td>
<td>150</td>
<td>ORR per RECIST v1.1 (INV-assessed) for the efficacy objective Relationship between PFS per RECIST v1.1 and various bTMB quantiles for the biomarker objective</td>
<td>PFS and DOR per RECIST v1.1 (INV-assessed) OS</td>
</tr>
<tr>
<td><strong>BFAST Phase II/III</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Cohort A ALK+</td>
<td>Alectinib 600 mg PO bid</td>
<td>78</td>
<td>ORR per RECIST v1.1 (INV-assessed)</td>
<td>DOR, CBR and PFS per RECIST v1.1 (INV-assessed) ORR, DOR, CBR and PFS per RECIST v1.1 (IRF-assessed) OS</td>
</tr>
<tr>
<td>Cohort B RET+</td>
<td>Alectinib 900 mg &amp; 1200 mg dose escalation</td>
<td>52-62</td>
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<td>DOR, CBR and PFS per RECIST v1.1 (INV-assessed) ORR, DOR, CBR and PFS per RECIST v1.1 (IRF-assessed) OS</td>
</tr>
<tr>
<td>Cohort C B+TMB+</td>
<td>Atezo 1200 mg IV q3w or platinum-based chemotherapy 46</td>
<td>410 (R: 1:1)</td>
<td>PFS per RECIST v1.1 (INV-assessed)</td>
<td>OS PFS, ORR and DOR per RECIST v1.1 (IRF-assessed) ORR and DOR per RECIST v1.1 (INV-assessed) 6- and 12-month PFS rates</td>
</tr>
</tbody>
</table>

*Cisplatin or carboplatin + pemetrexed for non-squamous histology, and cisplatin or carboplatin + gemcitabine for squamous histology. Administered per standard of care. INV, investigator; IRF, independent review facility; R, randomized; bTMB, blood Tumor Mutational Burden.

**Clinical trial identification:** MedOPP125 (NCT number in progress)

Legal entity responsible for the study: Medica Scientia Innovation Research-MEDSIR

Funding: Guardant Health Inc.

Disclosure: S. Viteri: Research: AbbVie, ARIAD, Astex, AZ/MedImmune, Boehringer, Clovis, CyRx, Daiichi Sankyo, GSK, Hanni, Incyte, Merck, Novartis, Pfizer, Puma, Roche, Servier, Vaxom. Advisor: Boehringer, Clovis, Idera Pharma, Novartis, Promega Biotech, Roche, Targovax. E. Felip Font: Personal fees (Consulting fees) from: Boehringer Ingelheim, Eli Lilly, Pfizer, Roche and MSD, Astra Zeneca and Bristol Myers Squibb. All other authors have declared no conflicts of interest.
Clinical Research platform Into molecular testing, treatment and outcome of non-Small cell lung carcinoma Patients (CRISP): a prospective German Registry to stage IV NSCLC AIO-TRK-0315) F. Griesinger1, W. Eberhardt2, N. Marschner3, M. Jänke4, A. Fleitz4, L. Spring4, J. Sahlmann5, A. Karatas6, A. Hipper6, W. Weichert7, M. Sebastian8, M. Thomas9 1Department of Internal Medicine-Oncology, Pius Hospital Oldenburg, University of Oldenburg, Oldenburg, Germany, 2Department of Medical Oncology, University Hospital Essen Westdeutsches Tumorzentrum, Essen, Germany, 3Oncology and Haematology, Praxis für interdisziplinäre Onkologie & Hämatologie, Freiburg, Germany, 4Clinical Epidemiology and Health Economics, XDINOCO AG, Freiburg, Germany, 5Data Management, Statistics & Medical Informatics, XDINOCO AG, Freiburg, Germany, 6AIO-Studien-gGmbH, AIO-Studien-gGmbH, Berlin, Germany, 7Institute of Pathology, Technical University Munich (TUM), Munich, Germany, 8Department of Oncology and Haematology, Universitätsklinikum Frankfurt (Johannes-Wolfgang Goethe Institute), Frankfurt am Main, Germany, 9Medical Oncology, Thoraxklinik Heidelberg, Heidelberg, Germany.

Background: Treatment in NSCLC is quickly evolving and new agents make it to the routine practice at a rapid pace. Whether outcome and PRO data generated from clinical trials with often narrow inclusion and exclusion criteria will hold up in the routine practice is of high interest, especially due to the increasing costs of new drugs. Therefore registry data are of ever increasing importance to patients, physicians and reimbursement institutions.

Trial design: We have started a prospective, clinical registry to document representative data on molecular testing, sequences of systemic therapies and other treatment modalities, and course of disease in patients with metastatic NSCLC in Germany (CRISP, NCT02622581). A particular focus is on molecular biomarker testing of patients before the start of first-line treatment. The data shall be used to assess the current state of care and to develop recommendations concerning topics that could be improved. PRO assessment will provide large-scale data on quality of life and anxiety/depression for real-life patients in routine practice. In addition, two questionnaires (concerning individual quality of life and patient-caregiver communication) will be validated in German patients with metastatic NSCLC. Furthermore CRISP will set up a decentral tissue annotation for future collaborative, investigational scientific biomarker testing. CRISP will be carried out in up to 150 representative cancer centers in all therapeutic sectors in Germany. More than 5000 patients will be recruited and followed up until death or for a maximum of 3 years. The first patient has been included in December 2015. Currently, 104 centers have been initiated, and 765 patients have been recruited. Preliminary data will be presented at the meeting in terms of molecular test rates, demographic data as well as treatment stratification in the 1st line setting. In conclusion: The registry CRISP will be the first to present representative real life data, covering all treatment settings of patients with NSCLC in Germany. CRISP is supported by AstraZeneca, Boehringer Ingelheim, BMS, Celgene, Lilly, MSD, Novartis, and Pfizer.

Clinical trial identification: NCT02622581
Legal entity responsible for the study: AIO-Studien-gGmbH, Berlin
Funding: AstraZeneca GmbH, Boehringer Ingelheim Pharma GmbH & Co. KG, Bristol-Myers Squibb GmbH & Co. KGaA, Celgene GmBH, MSD Sharp & Dohme GmbH, Lilly Deutschland GmbH, Novartis Pharma GmbH, and Pfizer Pharma GmbH.
Disclosure: F. Griesinger: Advisory Board/Honoraria: Ariad, Astra-Zeneca, Boehringer-Ingelheim, Bristol-Myer-Squibb, Celgene, Clovis, Lilly, Merck-Sharp-Dome, Novartis, Pfizer, Roche N. Marschner: ADB: Amgen, Roche Honoraria: Amgen, Celgene, Roche, research grants: Amgen, Celgene, stock ownership/leadership position: iOMEDICO AG. M. Sebastian: Advisory boards: IMS, MSD, Roche, Novartis, AstraZeneca, Boehringer, Celgene, Lilly, Pfizer. M. Thomas: Honoraria/AD Boards: IMS, BMS, Lilly, AstraZeneca, Roche, Pfizer, Celgene, Novartis. All other authors have declared no conflicts of interest.
Cancer cachexia (CAX), anorexia and muscle wasting (sarcopenia) in non-small cell lung cancer (NSCLC): an observational study in 531 patients

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Background: Since publications highlighting the role of sarcopenia, weight loss (WL) is no longer the corner stone of malnutrition assessment. An international consensus proposed in 2011 a definition and a staging of CAX, mainly based on WL, sarcopenia, inflammation and anorexia (Fearon). We initiated this study to fill the gap of epidemiological data on CAX in NSCLC in France and Belgium.

Methods: This cross-sectional, prospective multicentric study was conducted in Patients (pts) with NSCLC regardless of the tumor stage and the treatment line. Skeletal muscle mass (SMM) was assessed by analyzing LI CT-scan image. Pts completed Anorexia/CAX subscale of PAAC-T and EORTC QLQ-C30 health related quality of life (QoL) questionnaires. Primary endpoint was the frequency of CAX according to Fearon criteria. Secondary endpoints were the frequency and the characteristics of the other stages of CAX focusing on early and discrete malnutrition changes (pre-CAX).

Results: 539 NSCLC pts were recruited within the 3 months by 36 sites, analysis population was of 531 pts and 312 had SMM assessment. Median age was 66 years, 66.5% were males, 79.9% were PS ≤ 2, and the tumor stage was mainly IIB-IV (87.3%). 38.7% of pts had CAX, 33.8% pre-CAX and 0.9% refactory CAX. CAX was associated with molecular tumor profiles: 23.9% in patients EGR, ALK, ROS1, BRAF or HER2 positive, 41.4% in KRAS and 43.2% with no molecular abnormality (p < 0.003). Interestingly, the more advanced the CAX stage is, the poorer the score of functional QoL (except cognitive) of the QLQ- C30 questionnaires (p < 0.001). Sarcopenia was present in 66.7% of CAX pts and 68.5% of pre-CAX pts (all without WL or WL ≤ 2%). Notably, 25.8% of pre-CAX pts had only sarcopenia with limited WL (≤ 2%) and no anorexia (questioning the mechanisms of sarcopenia). In pts with limited WL (≤ 2%), the loss of appetite was associated with sarcopenia in 44% of the cases.

Conclusions: This is the first study showing an association between molecular abnormality in NSCLC and cachexia. It has also shown that it may be useful to detect sarcopenia in pts with limited WL (< 2%), especially in those with loss of appetite. Cachexia stages were associated to functional QoL items.

Clinical trial identification: NCT02968979, First received: November 17, 2016

Legal entity responsible for the study: Chugai Pharma France

Funding: Chugai Pharma France


Prevalence and recent time trend in aggressiveness of cancer care near the end of life: an expanded assessment in a cohort study

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Background: There is growing concern in society about aggressiveness of cancer care near the end of life (ACCEoL), mainly in metastatic disease. This study aims to determine prevalence and recent time trend of ACCEoL of adult cancer patients in a European country, comparing metastatic with others.

Methods: Cohort study of adults with ICD-9-CM diagnosis of cancer, who died in public hospitals in mainland Portugal (Jan’10 – Dec’15), identified from the Hospital Mortality database (HMD). HMD provided data on primary cancer site, presence of metastatic disease and primary outcome: a composite ACCEoL indicator aggregating presence of 1 of 14 individual indicators in the last 30 days of life or chemotherapy, immunotherapy or biological agents in the last 14 days of life (expansion of Earle et al. 2004 framework). We calculated the prevalence of composite and individual indicators and examined time trends (chi2 test for trend) for the whole cohort, in metastatic disease and for main primary cancers. We considered clinically meaningful > 5% change.

Results: 92,155 patients were included (median age 73 yo, IQR 62-81; 61.9% male; 53.0% metastatic). The prevalence of the ACCEoL was 71.1%, 69.9% in metastatic patients vs. 72.6% in others (p < 0.001), varying by primary cancer from 62.7% in breast to 79.3% in haematological (p < 0.001). The most prevalent individual indicators were > 14 days in hospital (42.7% 42.3% in metastatic) and surgery (27.8% 26.4% metastatic). The least prevalent were permanent tracheostomy (0.3%) and percutaneous gastrostomy (0.3%). Primary outcome remained stable overtime and despite some individual indicators showed statistically significant changes in study timeframe, none of these had > 5% change.

Conclusions: Surprisingly, we found unchanged trends of high ACCEoL among adult patients and no clinically meaningful difference for metastatic disease group. A lack of integrated palliative care, even with growing resources in the timeframe analysed, suggest that these have not been enough to reduce ACCEoL. The reduced ACCEoL in patients who died with slow progressive cancers (e.g. breast) suggests that better knowledge of disease trajectories can contribute towards reducing ACCEoL.

Legal entity responsible for the study: N/A

Funding: Calouste Gulbenkian Foundation, Liga Portuguesa Contra o Cancro - Núcleo Regional do Sul

Disclosure: All authors have declared no conflicts of interest.

Open-label randomized study of individualized pharmacokinetically (PK)-guided dosing versus body surface area (BSA) dosing of paclitaxel (PTX) in advanced non-Small Cell Lung Cancer (NSCLC)

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Background: Variability of PTX exposure using BSA dosing is well documented and often leads to severe toxicities. While carboplatin is dosed to obtain a specific exposure, paclitaxel is conventionally dosed by the BSA, leading to a wide range of exposure. This study compared PTX PK-guided dosing to BSA dosing in a PTX-carboplatin regimen treating stage III/IV NSCLC. This is the final analysis of interim results presented at ASCO 2015 (Poster #375). ClinicalTrials.gov: NCT02058433

Methods: 309 patients with stage III/IV NSCLC were randomized to receive up to 4 cycles of first line 3-weekly carboplatin (AUC 5) and a PTX dose of 175 mg/m² (Arm A), or a PTX PK-guided dose (Arm B) to achieve a time above a PTX plasma concentration of 0.05μM (T > AUC) for 26 to 31 hours. Response was classified according to Response Evaluation Criteria in Solid Tumors Group. PTX concentrations were measured using Liquid Chromatography Mass Spectrometry (LCMS).

Results: The median total dose of PTX was 2800 mg/m² (Arm A, n = 153) vs. 2600 mg/m² (Arm B, n = 156; p = 0.12). Arm B was associated with a significantly higher percentage of patients achieving a greater than 25% decrease in serum CEA > 12-15 months (p = 0.0018) compared to Arm A. Median (IQR) PFS was 6.2 (6.0) vs. 4.9 (4.3) months (p = 0.0006). Median survival was 16.0 (12.0) vs. 12.6 (9.0) months (p = 0.0006). Arm B was associated with a significantly lower rate of grade 3-4 neutropenia (14.7% vs. 18.6%; p = 0.0002) and febrile (9.6% vs. 12.9%; p = 0.025) neutropenic events.

Conclusions: PTX PK-guided dosing was associated with improved patient outcomes and toxicity profiles compared to BSA dosing of PTX in combination with carboplatin in stage III/IV NSCLC.

Acknowledgement: This study was supported by Salidas Biomedical, Inc.

Disclosures: All authors have declared no conflicts of interest.
measured by immunassay; T<sub>cortisol</sub> was calculated with PK software. The primary endpoint was reduction of grade 4 hematological toxicities.

**Results:** There were 164 patients in Arm A and 155 patients in Arm B, with 191 males and 128 females participating. PK-guided dose adjustment resulted in doses that were widely distributed (73–175 mg/m²), and statistically lower than in the BSA arm (by 24%, p < 0.001). Compared to Arm A, PK-guided dosing significantly reduced grade 4 neutropenia by 35% (p = 0.002, 23% vs. 16%) over 4 cycles. The incidence of severe (grade ≥ 3) neutropenia was also significantly reduced by 29% in Arm B over all cycles (p < 0.001). Additionally, neutropathy (≥ grade 2) was reduced from 20% in Arm A to 8% in Arm B (p = 0.008), representing a 60% reduction over all cycles. Response rates were not significantly different; objective response rates were 23% in Arm A and 29% in Arm B (p = 0.205); stable disease rates were 49% in Arm A and 42% in Arm B (p = 0.024).

**Conclusions:** Results of this study are in accordance with a previous report, and present further evidence that PK-guided dosing reduces severe toxicities. This is accomplished by an overall lowering of dose intensity, while still maintaining efficacy. PK-guided dosing personalizes chemotherapy, and may be useful in patient management.

**Clinical trial identification:** 02058433.

**Legal entity responsible for the study:** Tonji University Affiliated Shanghai Pulmonary Hospital, Tongji University

**Funding:** None

**Disclosure:** All authors have declared no conflicts of interest.

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**1390 PD**

**Prognostic impact of drug interactions in patients with advanced cancer**

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**Background:** The risk of drug-drug interactions (DDI) increases with the number of comedications. The prognostic impact of DDI in oncology is poorly understood.

**Methods:** We included 105 patients with advanced NSCLC, 100 patients with advanced ER-negative breast cancer (BC) and 100 hospice inpatients (HO) with advanced malignancies between 2010 and 2015. Data collected included all anticancer and non-anticancer drugs received, age, gender, presence of CNS metastases, smoking status, ECOG performance status (PS), Charlson comorbidity score and overall survival (OS) from the time of incurable cancer. Potential DDI were assessed using the hospINDEX of all drugs approved in Switzerland in combination with the DDI software - Bicycle mode (HCI Solutions, Bern, Switzerland). Primary study objective was to assess the prognostic value of the severity of DDI per patient cohort using Kaplan-Meier statistics, uni- and multivariate Cox regression models. The study had a power of 84% to detect a 25% survival difference at 25%.

**Results:** The median number of drugs was 5 (range 8 to 15) in all patients, lowest in BC (4) and highest in HO (6). A major risk for DDI was detected in 74 patients (24.3%) overall, including 29 NSCLC patients (27.6%), 25 BC patients (25.6%) and 20 HO patients (20%). The number of drugs was significantly associated with the risk of DDI (p < 0.001). The risk of a major DDI increased from 14% in patients with ≤4 drugs to 24% in patients with 4–7 drugs, 40% with 8–11 drugs and 67% in patients with ≥12 drugs. Median OS was 8.6 months in NSCLC, 33 months in BC and 12 months in HO. The severity of DDI was significantly associated with inferior OS in BC (HR = 1.34, p = 0.018), but not in NSCLC or HO. The severity of DDI remained significantly associated with OS in BC (HR = 1.34, p = 0.017) after correcting for patient age and ECOG PS.

**Conclusions:** Severity of DDI is a significant and clinically relevant prognostic factor in advanced BC, patients. Prospective trials should evaluate the potential benefit of avoiding polypharmacy in this group of patients. In the meantime, increased caution with polypharmacy seems warranted when treating patients with advanced cancer.

**Clinical trial identification:** 2016-00283 (BASEC, national trial identifier)

**Legal entity responsible for the study:** Markus Joerger MD-PhD ClinPharm

**Funding:** None

**Disclosure:** All authors have declared no conflicts of interest.

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**1390P**

**Efficacy of anamorelin in advanced non-small cell lung cancer (NSCLC) patients with anorexia/cachexia and modified Glasgow Prognostic Score (mGPS) of 2:** Pooled analysis of two phase 3 trials

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**Background:** Anorexia/cachexia occurs in patients with advanced NSCLC. In 2 randomized, double-blind, placebo-controlled phase 3 trials in cachectic NSCLC patients, the ghrelin receptor agonist anamorelin was well tolerated and significantly improved body composition parameters and anorexia/cachexia symptoms over 12 weeks (Temel JS et al, Lancet Oncol 2016). The mGPS (0–2) has independent prognostic value; patients with mGPS 2 have worse prognosis. This analysis determined anamorelin’s efficacy in cachectic NSCLC patients with mGPS 2 (C-reactive protein levels >10mg/L and albumin levels <3.5g/dL).

**Methods:** Stage III/IV NSCLC patients with cachexia (BMI< 20 kg/m² or ≥ 5% weight loss during prior 6 months) were randomized 2:1 to once-daily oral anamorelin 100 mg or placebo up to 12 weeks. An ad-hoc efficacy analysis was performed in the modified intent-to-treat population (N = 829) to assess whether mGPS score at baseline may predict differences in anamorelin treatment effect size at end of study (or last observation carried forward since week 6 or 9).

**Results:** Anamorelin treatment effect was statistically significantly better, compared with placebo, for all body composition parameters in all mGPS subgroups. This effect was numerically larger in patients with mGPS 2 and statistically significant, compared with placebo, for all analyzed parameters, except fatigue subscale score (Table). In patients with mGPS 2, the placebo-adjusted mean increase in body weight exceeded the 5% weight loss cutoff used as an official criterion for cancer cachexia diagnosis.

**Table: 1390P**

**Treatment Effect of Anamorelin in patients with mGPS 2 (n = 123)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean</th>
<th>95% CI</th>
<th>P value, compared with placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, kg</td>
<td>3.07</td>
<td>1.47–4.68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body weight change, %</td>
<td>5.40</td>
<td>2.82–7.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lean body mass, kg</td>
<td>1.84</td>
<td>0.62–3.06</td>
<td>0.003</td>
</tr>
<tr>
<td>Appendicular lean body mass, kg</td>
<td>1.04</td>
<td>0.32–1.77</td>
<td>0.005</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>1.35</td>
<td>0.38–2.31</td>
<td>0.007</td>
</tr>
<tr>
<td>Handgrip strength, kg</td>
<td>2.44</td>
<td>0.35–4.52</td>
<td>0.022</td>
</tr>
<tr>
<td>FAACT Anorexia/Cachexia subscale score</td>
<td>5.23</td>
<td>1.55–8.90</td>
<td>0.006</td>
</tr>
<tr>
<td>Fatigue subscale score</td>
<td>0.67</td>
<td>−3.24–4.58</td>
<td>0.736</td>
</tr>
</tbody>
</table>

**Conclusions:** In cachectic NSCLC patients with mGPS 2, anamorelin leads to significant improvements in body composition parameters and symptom burden. The extent of weight improvement in this population suggests that treatment with anamorelin may on average reverse pathologic weight loss.

**Clinical trial identification:** ROMANA 1: NCT01387269 ROMANA 2: NCT01387282

**Legal entity responsible for the study:** Helsinn

**Funding:** Helsinn

**Disclosure:** S. Kaasa: Stock ownership: Eir solutions AS. B. Laird: Advisory board membership: Chugai Pharma. R. Skipworth: Corporate-sponsored research: Research grant/agreement with Novartis. D. Currow: Unpaid advisory board member for Helsinn. Paid consultant and receive payment for intellectual property with Mayne Pharma and consultant with Specialist Therapeutics Australia Pty. Ltd. R. Giorgino: Helsinn Healthcare employee. All other authors have declared no conflicts of interest.
Background: Novel, complex, resource intensive, radiation technology is increasingly used for palliative therapy even though they are not cost effective in poor prognosis pts. (Kim HRB P 2015;536). Since nearly half of all radiotherapy (RT) activity is palliative (Hoskin Cl Onc 2013;531), objective, validated prognostic tools are urgently needed to guide cost effective utilisation of RT. As advanced cancer is associated with poor nutritional status and immune dysfunction, we assessed prognostic role of PNI which is based on serum albumin & peripheral blood lymphocytes.

Methods: Mortality of 233 unselected cancer pts treated over a 3 month at Nottingham was assessed. All tumour sites & histology were included. Overall Median age 68 yrs. Sites of RT field: Chest=29% Vertebrae=26% Pelvis=20% Brain=12% Limbs=6% Abd=3% Miscell=3% 95% completed RT as planned. 93% had stage 4 cancer. PNI available for 131 pts. Majority not suitable for systemic therapy following palliative RT; only 15% and 28% had further hormones and chemo respectively.

Results: Overall Median survival was 5.82 months; 38% died within 90 days of completing RT; Pts with low PNI (<38) had statistically significant higher 30 day and 90-day mortality (Table). On Cox regression, low PNI was strongly predictive of poor survival. (p<0.01; Exp(B) 0.338; 95.8% CI for Exp(B) 0.336 to 0.862). Pts who received systemic therapy following palliative RT had better survival. (Hormones and chemo P<0.001, Exp(B) 0.538; [95.0% CI for Exp(B) 0.336 to 0.862]. Pts who received systemic therapy following palliative RT had better survival.

Conclusions: For terminally ill cancer patients, who are not fit for further systemic therapy and whose PNI is <38, single fraction RT should be the standard of care.

<table>
<thead>
<tr>
<th>Table: 1391P</th>
<th>PNI</th>
<th>&lt;38</th>
<th>&gt;38</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age -Yrs</td>
<td>68</td>
<td>66</td>
<td>0.26*</td>
<td></td>
</tr>
<tr>
<td>Median RT dose - Gy</td>
<td>20</td>
<td>20</td>
<td>0.21#</td>
<td></td>
</tr>
<tr>
<td>Median No RT fractions</td>
<td>5</td>
<td>5</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>30 day mortality</td>
<td>10%</td>
<td>4%</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>90 day mortality</td>
<td>25%</td>
<td>15%</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Median Survival</td>
<td>3.21 mths</td>
<td>10.45 mths</td>
<td>&lt;0.001@</td>
<td></td>
</tr>
</tbody>
</table>

* T test; Mann-Whitney; Pearson Chi-Square; #Log rank.

1392P Characterization of cachectic patients with non-small cell lung cancer (NSCLC) according to their modified Glasgow Prognostic Score (mGPS)

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Background: Patients with advanced NSCLC often develop anorexia/cachexia, a comorbidity characterized by decreased body weight or low body mass index (BMI), which negatively impacts quality of life and life expectancy. Weight loss and BMI were suggested to have independent prognostic value (Martin L et al, JCO 2015). The mGPS (0–2) has independent prognostic value, where patients with mGPS 2 (C–reactive protein levels >10mg/L and albumin levels <3.5g/dL) have worse prognosis. Here, we investigated the characteristics of NSCLC patients with cachexia according to their mGPS, and whether mGPS can be used to differentiate patients with cachexia.

Methods: Patients with unselectable stage III/IV NSCLC and cachexia (BMI <20kg/m2 or >5% weight loss during prior 6 months) were enrolled in two phase 3 studies of the ghrelin receptor agonist anamorelin (ROMANA 1 and ROMANA 2). A pooled post-hoc data analysis was performed in the modified intent-to-treat population (N = 829), irrespective of treatment arm, to investigate the baseline characteristics of patients with mGPS 0–2.

Results: At baseline, 36% patients had mGPS 0 (n = 296), 49% mGPS 1 (n = 396) and 15% mGPS 2 (n = 123). Patients who lost >10% body weight during the prior 6 months had mainly mGPS 0–1; in contrast, among patients who lost >10% body weight, a higher percentage had mGPS 2. Patients with mGPS 2 had on average substantially lower values of body weight, body composition parameters, handgrip strength and anorexia/cachexia and fatigue scores than the other mGPS subgroups (Table).

Conclusions: While patients with cachexia present mGPS scores that vary from 0–2, a higher percentage of patients with mGPS 2 was observed among those with >10% body weight loss. The baseline characteristics observed in patients with mGPS 2 are worse than in the other mGPS subgroups, suggesting that mGPS may be helpful in identifying patients with more-advanced cachexia.

Clinical trial identification: ROMANA 1: NCT01387269 ROMANA 2: NCT01387282
Legal entity responsible for the study: Helsinn
Funding: Helsinn

<table>
<thead>
<tr>
<th>Table: 1392P</th>
<th>Baseline characteristics based on mGPS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>mGPS 0 (n = 296)</td>
<td>mGPS 1 (n = 396)</td>
</tr>
<tr>
<td>Body weight loss, n (%)</td>
<td>205 (43.0)</td>
</tr>
<tr>
<td>Mean body weight, kg (SD)</td>
<td>66.9 (13.66)</td>
</tr>
<tr>
<td>Mean lean body mass, kg (SD)</td>
<td>44.9 (8.64)</td>
</tr>
<tr>
<td>Mean appendicular lean body mass, kg (SD)</td>
<td>19.3 (4.59)</td>
</tr>
<tr>
<td>Mean fat mass, kg (SD)</td>
<td>19.4 (8.06)</td>
</tr>
<tr>
<td>Mean handgrip strength, kg (SD)</td>
<td>32.2 (11.74)</td>
</tr>
<tr>
<td>Mean FAACT Anorexia/Cachexia subscale score (SD)</td>
<td>31.6 (7.92)</td>
</tr>
<tr>
<td>Mean fatigue subscale score (SD)</td>
<td>32.4 (9.74)</td>
</tr>
</tbody>
</table>

FAACT, Functional Assessment of Anorexia/Cachexia Therapy; mGPS, modified Glasgow prognostic score; SD, standard deviation.
Previous palliative care encounter is associated with lower total terminal hospital charges and shorter length of stay in patients with metastatic cancer

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Background: Patients with metastatic cancer require substantial health care resources. Palliative care has been increasingly recognized for improvement of quality of life and reducing healthcare costs. Here, we examined the effect of prior palliative care encounters on the total hospital charges (TOTCHG) and length of stay (LOS) during the subsequent hospitalization.

Methods: We used National Inpatient Sample (NIS) 2014 to extract data for patients non-electively hospitalized with corresponding IC9D code of previous palliative care visit (IC9D code V667) and metastatic cancer. NIS is a nationally representative survey of hospitalizations conducted by Healthcare Cost and Utilization project. It represents 20% of all hospital data in the US. Univariate regression screening (threshold P > 0.1) and hybrid selection were used to create multivariate regression models. Relationship between TOTCHG and previous palliative care encounter as well as LOS and previous palliative care encounter were analyzed by using established models.

Results: A total number of 136591 patients admitted non-electively with metastatic cancer was identified among which 24736 had been coded for previous palliative care encounter at the time of admission. Among these patients, 28% had a previous palliative care encounter. Teaching hospital admission, rural hospital admission, self-pay, increased age and increased Charlson score were associated with higher rate of previous palliative care encounter. The multivariate regression model for LOS and previous palliative care visit were adjusted for survival outcome, number of procedures during hospitalization, number of previous chronic conditions, and number of the diagnosis during hospitalization. The model for TOTCHG and previous palliative care visit were adjusted for survival outcome, number of procedures and length of stay. We found that previous palliative care encounter was associated with lower total hospital charges (P < 0.0001) and shorter length of stay in patients with metastatic cancer (P < 0.0001).

Conclusions: Prior palliative care visit has been associated with decreased length of stay and total hospital charges. Future studies are needed to determine if early outpatient palliative care encounter will especially benefit patients with certain tumor types.

Legal entity responsible for the study: Yuzhou Liu

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Specialized ambulatory palliative care: (SAPV) 5-year results of a multi-professional care model by HomeCare linkern Niedererie, gGmbH (HC) in the Lower Rhine region

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Background: In recent times, German legislation has given terminally ill patients the right to receive SAPV, a multi-professional palliative care model which is aimed at prevention of hospital admission and enabling patients to die at home despite severe symptoms and a high need for palliative care. This new type of care raises the question about the best implementation and impact of SAPV. HC provides SAPV to 560.000 inhabitants of the city of Monchengladbach and the district of Viersen.

Methods: Data collected during daily care from 2012 to 2016 are summarized and analysed in order to describe the implementation and results of SAPV.

Results: 1798 patients were treated in 5 years. The first contact with SAPV was initiated by a GP in 30% of patients and by a specialist in 4.5% in 26% through a hospital, in 6% by a palliative care unit and in at least 30% by non-medical participants, such as relatives, nursing services, counseling centers etc. 20% of all patients were treated only temporarily by SAPV. 6% were admitted to a hospice, 14% were transferred to regular care after counseling or crisis intervention. Of the remaining patients, only 5.3% had to be hospitalized at the end and 96.7% were able to remain in their chosen home environment. That was at home for 80%, at a relative’s home for 3%, in a nursing home for 14%, and miscellaneous for the remaining 3% of patients. Sonography, thoracic and abdominal paracentesis, patient controlled analgesia were performed in the patient’s home by the SAPV team. Of all 1798 patients, 112 had to be hospitalized, 64 were subsequently retreated with SAPV and 48 were not. The main reasons for hospitalization were palliative interventions due to leuis and urinary retention in the upper tract, radiation of a fracture, psychosocial decompensation of the supporting relatives and confirmation of the palliative care. The average treatment duration was 19 days, the median was under 10 days. In detail, 112 patients were treated for less than 24 hours, 271 patients for less than 48 hours, 37 patients were treated for more than 90 days and 4 patients for over 200 days.

Conclusions: The wish of patients to die at home and to avoid unnecessary hospitalization can be achieved with this model of specialized care. Further comparative investigations are necessary to identify the optimal implementation and impact of SAPV.

Legal entity responsible for the study: Ulrich Grabenhorst

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Increasing palliative interventions at the end of life: patterns in metastatic colorectal cancer (mCRC)

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Background: Advances in chemotherapy for mCRC have improved median survival to more than 24 months. This has resulted in increased opportunity to undergo more frequent interventions for symptom relief at the end of life. We explored patterns of palliative interventions (surgery, endoscopy, interventional radiology (IR), drainage procedures, radiotherapy) in mCRC patients over a time of evolving chemotherapy regimens.

Methods: A retrospective review was undertaken of all mCRC patients referred to palliative care at a tertiary cancer center in Toronto, Canada. Patients treated 2000–2004 (early cohort) were compared to 2006–2010 (later cohort) as more effective palliative chemotherapy was available in the later time period. Descriptive statistics, t-tests, and chi-squared tests were employed.

Results: A total of 542 (212 early and 330 later cohort) patients were included. Compared to the early cohort, the later cohort was significantly younger (62 vs 65 years, p = 0.012), had more Stage 4 disease (47 vs 42%, p = 0.029), fewer curative surgeries (58 vs 70%, p = 0.005) and fewer had adjuvant chemotherapy (26 vs 38%, p = 0.002). Palliative care referral was delayed for the later cohort with longer times between diagnosis of unresectability and referral (13 vs 8 mths, p = 0.009) and shorter times between referral and death (6 vs 11 mths, p = 0.012). More patients in the later cohort had palliative surgery (31 vs 22%, p = 0.015), palliative IR procedures (15 vs 4%, p < 0.0001) and did not receive any chemotherapy (44 vs 29%, p = 0.001). The later cohort underwent more interventions in the last months of life with more chemotherapy and drainage procedures closer to death (7 vs 12 mths, p = 0.002 and 2 vs 9 mths, p = 0.006 respectively). There was no difference in survival (calculated from date of diagnosis to death) between the cohorts (median survival 35 months).
Chronic pleural effusion in malignancy: A single center’s ten years expertise with indwelling pleural catheters

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Background: Chronic and recurrent pleural effusion (PPE) in malignant diseases is a common cause of dyspnea, cough and chest pain. The vast majority is malignant pleural effusion (MPE), nevertheless disease-associated but not directly disease-caused parapneumonic pleural effusions (PPE) have also been described. Talc pleurodesis had been the only treatment option for decades, while for 20 years indwelling pleural catheters (IPC) have emerged as an alternative leading to spontaneous pleurodesis without any chemical agent in 40-50%.

Methods: Our aim is to explore patient characteristics, procedural variables and outcomes in a large population of patients with IPC due to PE in malignancy. Further, our objective is to identify factors associated with outcome.

Results: From 2006 until 2016 448 IPC were inserted in 395 patients, 52 received bilateral drainages (12.7%). 77.0% of the effusions were malignant (n = 304), 14.9% parapneumonic (n = 59), in 8.1% the etiology could not be clarified (n = 32). The most common underlying diseases were ovarian cancer (30.6%, 121 patients), lung cancer (23.0%, 91 patients) and breast cancer (11.4%, 45 patients). The median length of insertion was 1.2 months (0.03-23.6), the median survival time after insertion 2.4 months (23.0%, 91 patients) and breast cancer (11.4%, 45 patients). The median length of insertion was 1.2 months (0.03-23.6), the median survival time after insertion 2.4 months (23.0%, 91 patients). Spontaneous pleurodesis was observed in 26.6% (128/448 catheters) and was significantly associated with overall survival (HR 0.54, 95%-CI 0.39-0.75, p < 0.001). The most common complications were superficial infections (n = 14), empyema (n = 11; 1 grade 5 complication) and mechanical obstruction of the catheter (n = 13).

Conclusions: In conclusion, our retrospective series is the largest to date to report on IPC in malignancy and showed a manageable safety profile. Spontaneous pleurodesis was significantly associated with survival.

Legal entity responsible for the study: Charité Universitätsmedizin Berlin

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Conclusions: In their final months of life, palliative mCRC patients are undergoing more interventions requiring multi-disciplinary input with the aim of improving quality of life than previously. Increasing use of interventions in the last months of life has significant ramifications for previously, service provision, staffing and funding.

Funding: PSI Foundation

Disclosure: All authors have declared no conflicts of interest.
Fluctuating cancer screening uptake in France: results of the 5th EDIFICE survey

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Background: The EDIFICE nationwide surveys assess attitudes to cancer screening in France. All 5 self-reported surveys (2005, 2008, 2011, 2014 and 2016) focused on breast (BC), colorectal (CRC), prostate cancer (PC) screening; the 4th and 5th editions also included cervical (CC) and lung (LC) cancer screening.

Methods: The 5th survey recruited a representative sample of 1299 subjects (men [M], women [F], age, 50-74 y; no history of cancer) and focused on target populations of the national screening programs for BC and CRC (50-74 y), and on specific subpopulations for PC (M, 50-75 y; and F, 50-69 y) and LC (M and F, 55-74 y) screening. Participants were questioned about uptake of at least one lifetime screening test and compliance to recommended intervals. Data analysis encompassed nationwide screening programs, opportunistic screening, and vulnerability assessments (by the EPICES score).

Results: Rates for at least 1 lifetime BC screening test (screening rate) were 93%/94%/95%/97%/98% in 2005/2008/2011/2014/2016, respectively. In line with recommendations, 75%/83%/85%/81%/79% women reported having had a mammogram in the past 2 years (completion), with a significant drop in 2016 to 2014 (P=0.02). Vulnerability had a negative impact on compliance in 2016, though not previously. For CRC, screening rates were 36%/49%/50%/49%/42%, with the 2016 survey showing a significant decline, notably among unemployed (P=0.01). PC screening uptake was observed (99% in 2014 vs 94% in 2016, P=0.05), and women reported potentially higher rates of use compared with men. Compliance (FOBT or FIT in the past 2 years) increased steadily from 7%/5% (2005) to 33%/4% (2016), and rose significantly to 38% in 2016 (P=0.02). The rise was mainly observed in the 50-54 y age group, among men, and in non-vulnerable subjects. In 2016, a significant drop in overall CC screening uptake was observed (98% in 2014 vs 94% in 2016, P<0.01), particularly among unemployed women (98% in 2014 to 92% in 2016, P=0.05). Figures for at least 1 lifetime PC screening test were 56%/49%/50%/49%/42%, with the 2016 survey showing a significant decline, notably among unemployed (P=0.02) and non-vulnerable populations (P=0.05). LC screening rates (M,F) remained stable between 2014 and 2016.

Conclusions: In 2016, compliance to national programs was seen to be too high for BC screening (despite a decline), and on the rise for CRC, possibly due to the use since 2015 of the new FIT test. Although a national program is due to be implemented in France, uptake of CC screening is on the decline.

Legal entity responsible for the study: Kantor Health

Funding: Roche France

Disclosure: S. Couraud, L. Grellier, J-Y. Blay, A. Cortot, J-F. Morere, F. Esingier. Received honorarium fees from Roche/Edifice surveys were funded by Roche S.A. C. Lhomel. Employee of Roche. All other authors have declared no conflicts of interest.

Community-based lung cancer screening of high-risk population with low-dose computed tomography in China

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Background: Low-dose computed tomography (LDCT) screening for lung cancer has been recommended for high-risk individuals meeting the National Lung Screening Trial (NLST) criteria. However, there still is a debate concerning respective recommendations for Asian countries. Meanwhile, the proper duration and interval for lung cancer screening remains uncertain.

Methods: From November 2013 to July 2016, participants from Xuhui district of Shanghai were aged 45-70 years, and either of the following risk factors: 1) smoking history ≥20 pack-years, and, if a former smoker, had quit within the past 15 years; 2) a personal history of lung cancer; 3) personal cancer history; 4) professional exposure to carcinogens; 5) long term exposure to second-hand smoke; 6) long term exposure to cooking oil fumes. The eligible participants were randomly assigned to a screening arm with two rounds of alternate years LDCT screening and a control arm.

Results: A total of 6699 eligible participants were enrolled, 3147 participants were randomly assigned to control arm, 3512 were assigned to LDCT prevalence screening (51), of which 1516 participants underwent the second round of LDCT screening (S2) in the alternate year. Positive screening results were observed in 849 (24.2%) participants in S1 and 380 (28.0%) in S2. 80 (2.3%) cases were highly suspected of lung cancer in S1 and 31 (2.0%) in S2 according to the suggestions from multiple disciplinary team. By April 2017, lung cancer was diagnosed in 44 participants (1.3%) after S1, 12 (0.8%) after S2, and 10 (0.8%) in the control group (stage 0 to I 97.7%, 91.7% vs 20%; stage II to IV 2.3%, 8.3% vs 80%). Only 18 (32%) of these 56 lung cancer patients detected by LDCT would have qualified as NLST high-risk patients. There were 2 lung cancer-specific deaths in control group, whereas none in the screening arm participants.

Conclusions: LDCT screening increased the detection of early-stage lung cancer and reduced lung cancer-specific mortality. In China, lung cancer CT screening may also benefit patients outside the whole screening programme. LDCT screening done at biennial intervals could be taken into consideration due to few advanced-stage diseases.

Legal entity responsible for the study: Shanghai Chest Hospital

Funding: Shanghai Municipal Commission of Health and Family Planning

Disclosure: All authors have declared no conflicts of interest.

Colorectal cancer screening by fecal immunochemical testing in Iran

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Background: Colorectal cancer (CRC) is the third-most common cancer in Iran. We aimed to measure the uptake and feasibility of a pilot CRC screening programme based on fecal immunochemical test (FIT) in population aged between 45 and 75 years and the implications for scaling-up at the national level.

Methods: This pilot study was conducted in Tehran and individuals aged between 45 and 71 years in rural and urban areas were enrolled in the screening population. The FIT was offered by health navigators in primary health centers by collecting one single sample directly in to buffer kits by each participant. Health navigators aimed at increasing uptake and handled the whole screening programme from invitation to the referrals and provided the participants with information regarding the nature and importance of the CRC screening and details as to how to collect stool samples and send them back to the laboratory for analysis. If the first kit was not returned within 48 hours, a reminder call was sent. Those participants who had a positive FIT were referred to undergo a colonoscopy.

Results: A total of 1044 asymptomatic average-risk individuals were enrolled. The age mean was 54±1 and nearly 63.0% (n = 657) were female. Only small fraction of participants had awareness about CRC (13.7%) or polyps (8.3%) or screening tests (9.2%). Likewise their prior screening practice was extremely weak (2.2%). In multivariate regression analysis, awareness about CRC and screening tests significantly varied according to the ethnic groups, years of schooling, and family history of cancers (P < 0.05). In sum, 1002 returned the FIT kit, of which stool sample in six participants (0.6%) was deemed unsatisfactory for testing. The FIT uptake was 96.0%, the positivity rate was 9.1% and the detection rates were 11.9% for adenomas and 7.1% for advanced adenomas. No cancer was detected.

Conclusions: This is the first study on minimal quality metrics within a CRC screening process for the pilot phase and indicates that FIT modality as a test of choice is a safe and highly acceptable method of CRC screening in average-risk asymptomatic people. We suggest FIT as an initial CRC screening tool along with other preventive services in primary health care system in the nation.

Legal entity responsible for the study: Prof. Reza Malekzadeh

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Diagnostic Analysis of Patients Referred from General Practitioner with Serious Non-Organ-Specific Symptoms and Signs of Cancer: A Retrospective Cohort Study

**Background:** Recently, a diagnostic fast track for patients with serious non-organ-specific symptoms and signs of cancer was established in Denmark. For patients without cancer diagnosed within the first month, the prognosis is currently unclear.

**Methods:** A retrospective cohort study of 926 patients referred to Diagnostic Outpatient Clinic (DOC) at Herlev Hospital from April 2012 to December 2013. Baseline clinical parameters were collected from patient records. Time to cancer, death, cancer specific mortality (CSM), and death due to other causes were recorded until May 2016. 724 patients were identified without cancer one month after examination and divided into 2 subcohorts based on the initial assessment: true negatives (TNs; patients diagnosed without cancer at DOC and after 1 month) and false positives (FPs; patients referred from DOC but with cancer on the 1 month). Cumulative incidence of cancer, death, CSM, and death from other causes were estimated by the Aalen-Johansen estimator using 35 days after initial assessment as baseline.

**Results:** Clinical characteristics of the 724 patients: median age 65 years (range 17-92); 44% were men; 70% were referred from their general practitioner; 43% were former/current smokers; 18% were former/current alcohol abusers. The median age (p = 0.03) and comorbidity score (p < 0.01) were highest among the FPs. TNs vs. FPs had a lower risk of subsequent cancer (HR: 0.08; 95% CI: 0.05-0.13; p < 0.01), mortality (HR: 0.26; 95% CI: 0.16-0.41; p < 0.01) and CSM (HR: 0.07; 95% CI: 0.03-0.16; p < 0.01). Mortality from other causes was similar in the two groups (HR: 0.58; 95% CI: 0.29-1.19; p = 0.14). The negative predictive value (NPV) was 0.94 and the positive predictive value was 0.46. However, around 40% of the FPs were diagnosed with cancer within the first year.

**Conclusions:** Ruling out cancer by investigation at DOC was associated with low risk of subsequent cancer and the NPV was high. The FPs had higher risk of cancer, mortality, and CSM compared to the TNs.

Legal entity responsible for the study: Claus Larsen Feltoft

Funding: Department of Internal Medicine, Herlev and Gentofte Hospital (no specific grant number); Danish Cancer Society (grant number: R152-A9695-16-S7).

Disclosure: All authors have declared no conflicts of interest.

Increased Mutation Burden in High-Risk Lung Tissues: Toward Precision Cancer Risk Diagnosis

**Background:** Mutations are believed to accumulate in normal tissues at extremely low levels as a result of exposure to various carcinogenic factors. The degree of accumulation, namely mutation burden, is likely to be associated with cancer risk. However, owing to the limits of current detection methods for such extremely low frequency mutations, the mutation burden present in normal human lung tissues has been unclear. To overcome this limitation, we established a novel method for the quantification of extremely low frequency mutations in DNA samples. Using this method, we aimed to reveal the presence of mutation burden in normal lung tissues and its association with cancer risk.

**Methods:** Somatic mutations were quantified in normal lung tissues without smoking history (n = 11) (“entirely normal lung tissues” group), normal lung tissues with smoking history (n = 11) (“smoking-exposed normal tissues” group), and non-cancerous lung tissues of patients with lung cancer and smoking history (n = 11) (“smoking-exposed non-carcinogenic tissues” group). A sequence library (15,724 bases of 291 regions of 55 cancer-related genes) was prepared by multiple PCR using 100 DNA molecules. Libraries were sequenced using a next generation sequencer.

**Results:** The mutation burden in G3 (2.7 ± 0.8 × 10^−4 mutations/base) was significantly higher than that in G1 (1.8 ± 0.5 × 10^−5 mutations/base) (p = 0.0189). Accumulation of somatic mutations tended to be associated with increased cancer risk (OR = 3.75, 95% CI = 0.54–26.046). C-T mutations were significantly more frequent in G2 and G3 than in G1, which is in accordance with reported mutation signatures in cancer tissues [Alexandrov et al, Science, 354(2016)]. GCC and CCG were CTC mutations, signatures of exposure to the nitrosamines contained in tobacco smoke, were significantly enriched in G2 and G3.

**Conclusions:** To the best of our knowledge, this is the first study showing that mutations accumulate in high-risk lung tissues due to exposure to tobacco smoking. This will lead to a novel approach to precision cancer risk diagnosis.

Legal entity responsible for the study: Toshikazu Ushijima

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Change of natural history of hereditary diffuse gastric cancer after identification of a novel CDH1 mutation

**Results:** A novel genotypic variant in CDH1 c.48G>A (p.Q16Q) was identified in 28 family members, 16 male/12 female. Prior to variant identification, 6 obligate carriers were diagnosed with an advanced DGC, median age 56 (53–62) years and all died of the disease. After genetic testing, 8 symptomatic carriers were found early-stage DGC in the PTG specimen, median age 25 (19–59) years. Age-specific frequency of DGC in carriers according to PTG is shown in the Table.

**Table:**

<table>
<thead>
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<th>Age</th>
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<td></td>
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</tr>
<tr>
<td>61–70</td>
<td>1</td>
<td>40%</td>
</tr>
</tbody>
</table>

Histopathological RGB and PTG correlation was performed in 17 carriers attended at our institution (May 2013–Sept 2015). Median age at PTG was 54 (19–63) years. All pre-operative RGB were negative; one, which identified a single milimetric DGC focus, PTG specimens revealed one Tis and six T1a DGC, conferring RGB a predictive negative value (PNV) of 66% for DGC. Stage I A DGC had a median of 2.8 focigastroscopy, localized in the body (83%) and antrum (17%), with average diameter 0.73 mm and e-cadherin expression in 100% of the focig. No severe postoperative morbidity was recorded after a median follow-up of 29 (16–44) months.

**Conclusions:** PTG has changed the natural disease history in c.48G>A CDH1 carriers. Endoscopic RGB showed a low PNV for DGC and PTG is still highly recommended. More reliable screening methods are required in order to delay PTG in CDH1 mutation carriers.

Legal entity responsible for the study: Vall d’Hebron Hospital

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Cervical cancer screening in France: recent change in behaviors

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Background: Cervical cancer (CC) is the fourth most common cancer in women in France. Human papillomavirus vaccination and screening are complementary secondary prevention measures against CC. Screening by conventional PAP smear is recommended every three years for women aged 25-65y.

Methods: The EDIFICE nationwide observational surveys assess population attitudes to cancer screening in general. Representative samples of the French population aged 50-75 years are interviewed by phone using the quota method. Although the French CC screening program covers all women aged 26-65y, the present analysis pertains to a sub-population aged 50-65y (N = 356 in 2014 and N = 460 in 2016). Interviewees, with no personal history of cancer, were asked if they had ever had a smear test during a gynecological exam. The date of the last test was noted. Data analysis focused on age group, socioprofessional categories (SPC) and social vulnerability (defined by the EPICE score).

Results: In 2016, 94% of interviewees reported at least one lifetime smear test vs. 99% in 2014 (P<0.01). In line with current interval recommendations, 74% in 2016 and 75% in 2014 (P=0.81) had had the latest test done in the past three years. Younger age groups were significantly more likely to be compliant with the recommendations in 2014 (P<0.01) than not in 2016 (P=0.18). SPC also had a significant impact on compliance rates in 2016 (P<0.01) but not in 2014. Vulnerable women were less likely to be compliant at the latest exam: this trend was non-significant in 2014 (98% vs 100% in non-vulnerable, P=0.14) but significant in 2016 (98% vs. 97%, P=0.01). Vulnerable women were also significantly less likely to be compliant with the recommendations (64% vs 83%, P=0.01 in 2014; 63% vs. 79%, P=0.01 in 2016).

Conclusions: Between 2014 and 2016, participation in CC screening decreased and compliance rates stagnated. Compliance with screening recommendations was negatively affected by the following: unemployment, low SPC or classification among vulnerable populations. Additional analysis will further investigate these findings, which highlight the need for generalized population-based screening programs and targeted actions for non-participants, as advocated earlier this year by the French National Cancer Institute (INCa).

Legal entity responsible for the study: Kantar Health

Funding: Roche

Disclosure: T. de la Motte Rouge: Consultancy work AstraZeneca, Roche, MSD, Pfizer. Corporate-sponsored activities for non-participants, as advocated earlier this year by the French National Cancer Institute (INCa).

Genetic counseling, screening and risk reducing practices in patients with BRCA mutations

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Background: Worldwide practices of genetic counseling remain variable. We present genetic counseling, mammography and MRI screening & risk-reducing surgeries on patients with BRCA mutations & VUS of our BRCA mutations study (El Sagh et al, Oncologist 2015).

Methods: Chart review & phone calls for collection of information were done on 45 pts over the past 250 pts tested. IRB approval obtained. 14 pts (5.6% of total) with deleterious mutations & 31 pts (12.4% of total) with VUS were included. 7 pts had metastatic breast cancer. 4 pts were not reachable. We present results on 33 pts for whom we collected information about genetic counseling, screening, Contralateral Prophylactic Mastectomy (CPM) & Risk Reducing Salpingo-oophorectomy (RRSO).

Results: 14 pts with deleterious mutations (7 BRCA1 & 7 BRCA2 positive pts) & 19 pts with VUS mutations (4 BRCA1 & 16 BRCA2). 1 pt had both BRCA1 & BRCA2 were examined. Of the 14 pts with BRCA deleterious mutations, 57.14% (8/14) said they received some genetic counseling from their own oncologist and not a specialized genetic counselor. 85.71% (12/14) were undergoing regular screening mammogram, 35.71% (5/14) are undergoing regular screening breast MRI. 50% (7/14) underwent CPM & 57.14% (8/14) underwent RRSO. Also, 57.14% (8/14) advised their family members to undergo BRCA mutation testing.

Conclusions: The majority of pts with BRCA mutations continue to undergo screening mammography & breast MRI. Only 50% of pts with BRCA deleterious mutations underwent CPM & 60% RRSO, while a few pts with VUS mutations underwent CPM & RRSO. Genomic counseling is mostly done by medical oncologists. Our data supports recommendations to include genetic counseling in the training and Continuing Medical Education CME of Oncologists, and to improve patient education. More importantly, there is an urgent need for more certified professional genetic counselors in Lebanon & worldwide.

Legal entity responsible for the study: Naji El Sagh

Funding: None

Disclosure: All authors have declared no conflicts of interest.

NGS and Sanger screening for BRCA1/BRCA2, CHEK2 and TP53 in Argentine high-risk breast/ovarian cancer families and bioinformatic studies: Initial results

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Background: In this study, we aimed at reporting the frequency of BRCA1, CHEK2 and TP53 mutations in our high risk breast/ovarian cancer population, in order to determine the role of these genes testing in breast/ovarian cancer risk assessment.

Methods: Total DNA of 484 unrelated cases and 180 relatives were sequence using either Sanger (564) or NGS (100) for BRCA1/BRCA2, CHEK2 and TP53 mutations. While 64.3% (312/484) of the population studied belong to Jewish ethnicity, the remaining patients were european-americans.
Results: Of the 484 probands analyzed, 15.9% were BRCA1/BRCA2 mutation carriers, 9.7% in BRCA1, 6% in BRCA2 and one patient was double heterozygous. Overall, 18.9% of the Jewish patients presented Ashkenazi founder mutations and 9.9% of European-American-Jewish patients was positive for BRCA1 mutations. The c.667delAC was the most frequent alteration, representing 34.2% of all mutations identified. Pathogenic variants in CHEK2 and TP53 genes were present in 4% and 1% of our European-American-Jewish cases. Eighteen pathogenic variants different from Ashkenazi panel were identified in BRCA, three were novel and twelve not previously reported in argentinian population. Twenty-seven variants of uncertain significance were found. Conclusions: An association between genetic ancestry and mutational profile was observed only in the Jewish population. The 66.7% of the pathogenic variants found in our non-Jewish cohort were in BRCA2. Our results confirm the high level of admixture present in argentinian population, and highlight the detection of novel variants that could be typical of our region. The knowledge of them is relevant to improve patient risk assessment.

Legal entity responsible for the study: National Asociation of Cancer Geneticists, Buenos Aires, Argentina

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1419P Clinical features and outcomes of reversible posterior encephalopathy syndrome following bevacizumab treatment

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Background: Reversible posterior leuкоencephalopathy syndrome (RPLS), also known as Posterior reversible encephalopathy syndrome (PRES), is a distinct clinicoradiological entity characterized by a constellation of clinical features, and a potentially devastating complication of bevacizumab treatment.

Methods: Patients were identified from the published literature using ‘PubMed’ databases using the terms ‘bevacizumab’ or ‘RPLS’ and ‘PRES’ from January 2006 to December 2016, who developed RPLS (RFES) features within 3 weeks of bevacizumab treatment, who had brain imaging findings of focal vasogenic edema and radiologic proof of reversibility.

Results: To date, a total of 22 cases of RPLS (RFES) following the administration of bevacizumab have been reported in the literature. The mean age at presentation of these patients was 50 years (range 34-74 years), 6 of whom were male and 14 female. Headaches (n = 11), seizures (n = 10), visual disturbances (n = 9) and nausea and vomiting (n = 8) were the common presenting symptoms. In a majority of patients, an increase in blood pressure from their baseline values was observed during their hospitalization. RPLS occurred in 3 patients who received bevacizumab as monotherapy and the rest had received bevacizumab in combination with other chemotherapeutic agents (oxaliplatin, n = 8; fluorouracil, n = 6; leucovorin, n = 5; gemcitabine, n = 3; paclitaxel, n = 3; capecitabine, n = 3; doxorubicin, n = 2; carboplatin, n = 2; and irinotecan, n = 1). In 20 out of 22 patients, PRES resolved following withdrawal of bevacizumab and strict control of blood pressure. 3 patients also received prednisolone and mannitol as part of their treatment for RPLS. However, 2 out of 22 patients could not recover from severe coma, and died.

Conclusions: A high level of suspicion for RPLS is advisable in patients who develop headache, seizures, visual disturbances, during bevacizumab treatment, either as monotherapy or in combination with other chemotherapeutic agents. These data support the need for close vigilance of neurological features and blood pressure monitoring of patients undergoing bevacizumab treatment. Prompt withdrawal of bevacizumab and blood pressure control appear to portend favorable outcomes in these patients.

Legal entity responsible for the study: OMC-BC

Funding: None

Disclosure: All authors have declared no conflicts of interest.
of the text and the qualitative analysis of the information was done with the support of the ATLAS ii software.

Results: We observed an improvement in the knowledge using analysis quantitative design. The Citizen’s Jury voted 11-2. Eleven women voted yes and two did not. Women thanks for it, but there are still ignorance and confusion about breast cancer screening. There are three reasons for voting yes, for their health, for the nature of the test and for their individual freedom. There are women who argue the lack of effectiveness and the cost to justify their negative vote to mammography, at least with a universal character. Women make proposals to policymakers related to improving information, psychological care and research.

Conclusions: Spanish women have a very positive attitude to breast cancer screening although the information transmitted changes the opinion of some women, who want informed decision making. They bet to maintain or increase the medicalization of their lives.

Legal entity responsible for the study: Dr. José Manuel Bauzá Cañada

Funding: Fundación Progreso y Salud de investigación biomédica. PI-0130-2014

Disclosure: All authors have declared no conflicts of interest.

1420P   Genetic landscape in HBOC families from Brazil: A mutational analysis

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Background: Even if 10% of breast cancers are diagnosed in the context of hereditary predisposition, for a great proportion of families the molecular mechanism of cancer predisposition remains unclear. Founder mutations with increased risk for breast and other cancers have been described in some Latin American countries, but the hereditary breast and ovarian cancer (HBOC) mutational landscape remains understudied. The current study targets a highly mixed genetic contributions. Our study aims to evaluate the contribution of germline BRCA1/2 and moderate penetrance genes mutations in the incidence of HBOC Brazilian families.

Methods: This is a retrospective analysis of a series of 66 consecutive patients with HBOC syndrome who underwent genetic test between March 2007 and March 2017 in Sirio-Libanês Hospital. Clinical, pathological and sequencing available data on mutations and unclassified variants were analyzed, moderate and low penetrance genes were considered.

Results: The majority of the patients were tested in the context of multigene NGS panels (69%), 205 of the patients had only access to BRCA1/2 full gene screening. A pathogenic mutational mutation was identified in 227 index cases (34%). Unclassified variants (UV) were present in 139 tests (19%). A pathogenic mutational mutation was identified in 227 index cases (34%). Unclassified variants (UV) were present in 139 tests (19%). BRCA1/2 mutations could explain the molecular mechanism of cancer predisposition in 133 cases (20%) while TP53 gene was the second most commonly mutated gene in our cohort (46 patients, 7%). 83% of TP53 mutations corresponded to the Brazilian TP53 founder mutation R337H (c.1012G>A).

Intermediate penetrance genes mutations were present in 22 cases (33%): 11 for PALB2, 6 for ATM, 4 for CHEK1, 1 for BRIP1. Mismatch repair genes were mutated in 3% of the patients. The index cases were in majority women (98%) diagnosed with breast cancer under 50 years (34%), 68 (10%) of them with bilateral breast tumors.

Table: 1420P

<table>
<thead>
<tr>
<th>Gene</th>
<th>Pathogenic mutations (n)</th>
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<tbody>
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<tr>
<td>BRCA2</td>
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<td>ATM</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>BRIP1</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>CHEK2</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>RAD51C</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>BARD1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>BAP1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>MLH1</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>MSH2</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>PMS2</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>MSH6</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>EPCAM</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BMPR1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Conclusions: For the majority of the patients the mechanism of predisposition remains unknown. All together BRCA1, BRCA2 and TP53 mutations could explain the predisposition of 27% of the index cases in our cohort.

Legal entity responsible for the study: Registro de Cáncer Hereditario Brasileiro

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1421P   Recommended cancer screening and vulnerable populations: results from the EDIFICE 5 survey

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Background: Based on data from the 2011, 2014 and 2016 EDIFICE surveys, we sought to identify potential links between impoverished living conditions and participation in screening in the context of organized programs (colorectal (CRC), breast (BC) and cervical cancers (CC)).

Methods: The EDIFICE observational phone surveys were conducted among representative population samples (age 40-75 yrs in 2011 [N = 1603] and 2014 [N = 1602]; age 50-75 yrs in 2016 [N = 1501]) using the quota method. Attitudes regarding screening were assessed in groups of individuals within the target age-groups for each screening program. Participation in screening and follow-up rates were assessed by asking if respondents had undergone at least one screening examination in their lifetime and within the recommended time frame (2 yrs for CRC and BC, 3 yrs for CC). Data were analyzed according to the validated EPICES vulnerability score.

Results: For CRC, over the period 2011/2014/2016, participation increased in non-vulnerable subgroups (60% vs. 63%, NS and 63% vs. 68%, P = 0.05) as did follow-up rates (34% vs. 39%, NS and 33% vs. 40%, P = 0.01). Participation (69%/54%/53%) and follow-up (31%/30%/31%) were stable among vulnerable individuals. Participation was lower in vulnerable vs. non-vulnerable individuals in 2014 (P = 0.02) and 2016 (P < 0.01). For BC, participation rates were stable over 2011/2014/2016, in non-vulnerable (97%/96%/98%) and vulnerable individuals (94%/96%/93%), but follow-up rates decreased (87%/85%/79% and 81%/76%/65%, respectively). In 2016, participation and follow-up rates were lower in vulnerable vs. non-vulnerable groups (P = 0.01, P < 0.01). Participation and follow-up were lower in vulnerable vs. non-vulnerable groups in 2016 (P < 0.01, P = 0.01).

Conclusions: The 2016 EDIFICE survey confirms the increasing impact of social vulnerability on recommended screening programs, particularly for CRC.

Legal entity responsible for the study: Kantar Health

Funding: Roche

Disclosure: J.-F. Moreere, F. Eisinger, J.-Y. Blay, S. Couraud, A. Cortot, L. Greillier: Honorary fees from Roche Edifice surveys were funded by Roche S.A. C. Lhomme: Employee of Roche Edifice surveys were funded by Roche S.A. All other authors have declared no conflicts of interest.
1422O CTCA toxicity scoring and EORTC quality of life questionnaire: A comparison of physicians’ and patients’ scoring of toxicity in the “Panther trial”


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Background: A debate on health-related quality of life (HRQoL) by patients' assessment and the assessment of toxicity by physicians in clinical trials is ongoing. The relations between these two assessments is therefore of importance. The aim of this study was to investigate the relations between toxicity items (Common Terminology Criteria for Adverse Events, version 3.0.) and items in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30).

Methods: Data was collected in a randomised phase 3 trial, comparing dose dense vs standard administration of adjuvant chemotherapy in high-risk breast cancer patients. A total of 1428 event-free patients were included. Relations between 13 toxicities and 36 EORTC QLQ-C30 items (some with more than one toxicity) were investigated.

Results: A total of 1428 event-free patients were included. Relations between 13 toxicities and 36 EORTC QLQ-C30 items (some with more than one toxicity) were investigated.

Table: 1422O Strong or moderate relation between toxicity and HRQoL item

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>HRQoL item</th>
<th>Relation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>q17: Have you had diarrhoea 0.53 (0.47 to 0.59)</td>
<td>Moderate relation (0.30-0.49)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>q15: Have you vomited? 0.50 (0.39 to 0.62)</td>
<td>Moderate relation (0.30-0.49)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>q10. Did you need to rest? 0.35 (0.28 to 0.41)</td>
<td>Moderate relation (0.30-0.49)</td>
</tr>
<tr>
<td></td>
<td>q12. Have you felt weak? 0.35 (0.28 to 0.41)</td>
<td>Moderate relation (0.30-0.49)</td>
</tr>
<tr>
<td></td>
<td>q18. Were you tired? 0.41 (0.36 to 0.47)</td>
<td>Moderate relation (0.30-0.49)</td>
</tr>
</tbody>
</table>

5 = Strong relation (0.50-1.00)
3 = Moderate relation (0.30-0.49)
There were no or weak relations between all the other toxicities and HRQoL items.

Conclusions: Few relations were found between CTCAE and HRQoL items, indicating that CTCAE does not mirror the total patient experience. Some toxicities, however, are not related to patients scoring of HRQoL and therefore have to be reported by physicians. These findings should raise concerns on how to best evaluate HRQoL/toxicities in clinical trials.

Clinical trial identification: NCT00798070 and ISRCTN0017665

Legal entity responsible for the study: Department of Oncology-Pathology, Karolinska Institutet

Funding: Swedish Cancer Society

Disclosure: T. Foukakis: Honoraria for lectures from Novartis, Pfizer, Roche and Eisai. Royalty from UptoDate. Institutional grant to the Karolinska University Hospital from Roche and Pfizer. M. Granit: Institutional research support from AstraZeneca, Roche, Novartis, Pfizer. Lecture fees & honoraria for advisory boards from Roche, AstraZeneca, Celgene, Novartis, OBI-Pharma, Amgen. Consultant for Acceleris. An immediate family member employed by Sandoz. G. von Minckwitz: Institutional research support from Pfizer, Sanofi, Amgen, Roche, Novartis, Celgene, Teva, AstraZeneca, Myriad Genetics, Abbvie, Vifor Pharma. N.-O. Bengtsson: Advisory board Amgen Biosimilars for Trastuzumab. G. Steger: Lecture honoraria and travel support from Amgen and Roche. J. Bergh: Grants from Amgen, AstraZeneca, Bayer, Merck, Pfizer, Roche and Sanofi-Aventis to Karolinska Institutet and University Hospital. No personal payments. Honoraria from UptoDate for a chapter in breast cancer diagnostics to Asklepios Medicine HB. All other authors have declared no conflicts of interest.

1423P Loneliness and cognitive dysfunction in elderly cancer patients

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Background: The number of geriatric cancer patients is progressively increasing. The evaluation of cognitive functions is important. Loneliness is an emotional experience that results from unmet personal or social requirements. The association between loneliness and cognitive dysfunction has been well documented in elderly patients. However, there is no data in elderly cancer patients. The purpose of this study is to evaluate the association between loneliness and cognitive dysfunction in geriatric cancer patients.

Methods: Patients, more than 65 years of age, in departments of medical oncology and geriatrics were included. Patients were tested with multidimensional Scale of Perceived Social Support (PSC), UCLA loneliness Scale (ULS), standardized mini mental state examination (SMMSE), Clock drawing test and geriatric depression scale (GDS). Results: 314 elderly patients (214 with a diagnosis of cancer and 120 without cancer) were evaluated. Scores of PSC, ULS, SMMSE were higher in patients without cancer. Median score of GDS in cancer patients was higher than non-cancer patients (4 vs 2, p < 0.001). The analysis of ULS and SMMSE showed a negative correlation between

<table>
<thead>
<tr>
<th>Table: 1423P</th>
<th>Risk Factor</th>
<th>High Loneliness Score</th>
<th>p</th>
<th>Cognitive Impairment</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of depression</td>
<td>1.98 (1.0-3.6)</td>
<td>0.02</td>
<td>2.64 (1.3-5.1)</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Low social support</td>
<td>2.01 (1.1-3.4)</td>
<td>0.01</td>
<td>1.1 (0.5-2.1)</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>Educational status - low</td>
<td>3.01 (1.3-6.6)</td>
<td>0.007</td>
<td>1.93 (0.8-4.4)</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>&gt;75 years old</td>
<td>1.46 (0.8-2.6)</td>
<td>0.21</td>
<td>1.36 (0.6-2.7)</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.24 (0.5-2.6)</td>
<td>0.56</td>
<td>0.88 (0.3-2.3)</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>High income</td>
<td>1.36 (0.7-2.4)</td>
<td>0.27</td>
<td>1.1 (0.6-2.2)</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>Retired</td>
<td>0.64 (0.2-1.4)</td>
<td>0.30</td>
<td>0.54 (0.2-1.4)</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>Cancer diagnosis</td>
<td>0.93 (0.5-1.6)</td>
<td>0.81</td>
<td>1.79 (0.8-3.6)</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>Live in Rural</td>
<td>1.61 (0.7-3.3)</td>
<td>0.20</td>
<td>1.5 (0.6-3.3)</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>Comorbidity</td>
<td>1.38 (0.68-2.8)</td>
<td>0.36</td>
<td>1.18 (0.6-2.2)</td>
<td>0.61</td>
<td></td>
</tr>
</tbody>
</table>

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loneliness and cognitive functions (r = −0.185, p < 0.001). The negative correlation was observed both in cancer patients (r = −0.206, p = 0.001) and non-cancer patients (r = −0.262, p = 0.002). In multivariate analysis, presence of depression, low PSC scores and low educational status were associated with high ULS score. In conclusion, analysis of factors associated with cognitive dysfunction concluded that depression was associated with increased risk of cognitive dysfunction. (RR: 2.64 (1.3-5.1), 95% CI, p = 0.004) (Table).

Conclusions: Elderly cancer patients, cognitive functions are negatively affected by increased loneliness. However, the association between cancer diagnosis, loneliness and cognitive dysfunction couldn’t be demonstrated in multivariate analysis.

Legal entity responsible for the study: Ali Aban

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1424P The study of emotional distress in oncology patients

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Background: A study of the levels of emotional distress in patients during diagnostics and hospitalization was conducted at Petrov Oncology Scientific Research Institute in 2016. The work presented analyzes the results of the study of emotional distress in oncology patients. Groups of oncology patients, who most acutely require professional psychological aid, have been allocated.

Methods: The study is based on the modified distress self-evaluation method of International Psycho-Oncology Society (IPOS).

Results: 4,113 patients have been studied in total, of them 2,113 at the stage of diagnosis and 2,000 during hospitalization. The percentage of outpatients who report an abnormal anxiety level on the self-evaluation scale is distributed among nosology as follows: breast – 22%, gynecology – 18%, urology – 16%, unspecified diagnosis – 13%, digestive tract – 11%, lungs – 7%, soft tissue and skin tumors – 5%, and bones – 4%. The analysis of the data distribution between in-patient departments has shown that, among the patients reporting abnormal anxiety levels, 21% are hospitalized in the breast tumors department, 16% in the gynecology department, 10% in the head and neck tumors department, 9% in the radiology department, while the chemotherapy, thoracic surgery and urology departments admit 8% each, 6% are in the oncohematological department, and 5% in the general oncology department during hospitalization.

Conclusions: More than 40% of oncology patients experience abnormal anxiety levels related to the disease, the treatment and related changes in lifestyle. The majority of patients who describe their anxiety as abnormal have breast cancer.

Legal entity responsible for the study: Kristina Kondrateva

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1425P Risk of mood disorders in long-term cancer survivors: A population-based cohort study

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Background: Evidence regarding whether long-term survivors (≥5 years) of adult cancers (LSAC) have a higher risk of mood disorders than the general population is not consistent. We aimed to compare the mood disorder rates between the two cohorts and to identify potential risk factors.

Methods: We conducted a retrospective population-based cohort study using the Taiwan National Health Insurance Research Database. We identified LSAC who were newly diagnosed between January 1, 2000 and December 31, 2007. One control was matched per patient for age, sex, index date, and the Charlson comorbidity index (CCI). The primary outcome was diagnosis of mood disorders during the follow-up period (incidence rate ratio (IRR)).

Results: We identified 190,748 LSAC and 190,748 controls. The mood disorder risk was 1.16, 95% confidence interval [CI] 1.13–1.18, P = 0.0001. Patients with certain cancer types were at increased risk, particularly in the first 2 years after diagnosis. However, patients with head and neck cancers or esophageal cancers had a higher risk after the 5-year follow-up period (incidence rate ratio = 1.40, 95% CI = 1.18–1.67; 2.46, 95% CI = 1.29–4.69, respectively). Multivariate analysis indicated that being female, aged 40–59 years, with more than two primary cancers, receiving two or more treatment modalities, having CCI scores higher than 3, a higher urbanization level, and lower monthly income were independently associated with an increased risk of mood disorders.

Conclusions: Long-term cancer survivors have an increased risk of mood disorders and therefore should be followed-up for depression especially in those with certain site-specific cancer types.

Legal entity responsible for the study: Wen-Kuan Huang

Funding: Chang Gung Medical Foundation, Chang Gung Memorial Hospital at Linkou

Disclosure: All authors have declared no conflicts of interest.

1426P What oncologists should know about the screening of psychological distress: One example of pilot study in Ancona

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Background: Screening for psychological distress is one of the most important steps in Psycho-Oncology research and clinical assistance. In our Institution, before the present study, four studies have been carried out in this area from 2013 to 2016: 441 people were screened and 981 questionnaires were administered.

Methods: The study has been carried out using the following tools: Needs Evaluation Questionnaire (investigates five areas: informative needs, needs related to assistance and care, relational needs, needs for psycho-emotional support, material needs); Beck Depression Inventory II (BDI II); both for caregivers and for patients; Mini Mental Adjustment to Cancer (MiniMac, for the copying style); State–Trait Anxiety Inventory–2 (for the expression of angst).

Results: From February to April 2017, 78 people have been screened (44 patients and 34 caregivers). Male/female ratio was 29/49; median age was 54 years (range 21-84); 32% of patients showed informative needs, 48% indicated a psychological need, 18% assistance needs. Depression was more present in patients (50%) than in the caregivers (22%) and problems concerning sleep (65%) and fatigue (60%) were more common; only 61% of patients had a fighting spirit while 24% of caregivers showed a high expression of angst. Fischer test showed a correlation between anxious preoccupation (MiniMac) and symptomatic depression (P = 0.0008432860); moreover, Helplessness hopeless copying style was also related (P = 0.00396666) to depression; caregiver’s expression of aggressiveness (P = 0.114394682) is to patients’ anxious preoccupation. The relationship between patients’ depression to caregivers’ aggressiveness requires further investigation (P = 0.24739974).

Conclusions: Psychological screening can fulfill the following aims: discover expressed needs, coping styles, depression, familiar distress, burden. The results and the correlations underline the importance of managing the patients’ anxiety and the expression of the caregivers’ aggressiveness and the relationship of such issues with depression. Moreover, informative needs are associated to the most diffused psychological needs.

Legal entity responsible for the study: Clinica Oncologica Ancona

Funding: Fondazione Rossetti-Federcoastante Ancona

Disclosure: All authors have declared no conflicts of interest.

1427P Biopsychosocial factors underlying older patients treated for an incurable cancer in a two-tiered health care system in Brazil

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Background: Patients with advanced cancer experience symptoms that include pain, fatigue, and depression. We sought to describe prevalence and identify factors associated with biopsychosocial distress in older patients (65+) diagnosed with cancer stage IV.

Methods: Participants were recruited from two different types of health care facilities, public (PUB) and private (PRI) institutions, in Brazil. A cross-sectional analysis of common biopsychosocial symptoms (anxiety, depression, pain, and fatigue), and quality of life reported by older patients undergoing chemotherapy treatment was performed.

Results: Older patients (n = 167) were enrolled (Mean age=73; SD = 5.6); 59.3% from PUB. Majority were female (56.3%; 38.9% PUB); while (68.8% 35.7% PRI p<0.01); married (59.3%; 32.1% PUB, p<0.01); and diagnosed with GI (29.9%; 15.8% PUB), GU (16.2%; 4.9% PUB), and hematologic (13.8%; 7.3% PRI) cancers. Almost 16% of patients reported depression symptoms (9.6% PUB) and 12% of anxiety (8.4% PUB). PUB patients also reported associated lower QOL, which is at 50th percentile of the US
norm (PRI is at 75th percentile). PUB patients reported significantly more biopsychosocial problems including distress (21.6% vs 7.2%), pain (28.1% vs 12.0%), fatigue (34.7% vs 16.8%), sleep (22.6% vs 15%), neuropathy (22.8% vs 8.4%), and financial toxicity (16.2% vs 5.4%), compared to patients treated at PRI (p < 0.05). Mostly pain (B = 1.8, B = 6.6), fatigue (B = 0.8, B = 6.3) and sleep (B = 1.2, B = 8.3) were associated with moderate to severe distress and worst QOL (all p < 0.01).

Conclusions: Older patients with late-stage cancer in Brazil suffer substantial unrecognized biopsychosocial problems and their QOL is lower than that of younger patients. The difference in QOL between older and younger patients should be included in quality cancer care. Moreover, patients treated within PUB show worse outcomes than PRI counterparts, and they are at higher risk for multiple physical, psychological, and financial morbidity. Earlier identification of biopsychosocial screening with appropriate supportive care may improve their QOL.

Legal entity responsible for the study: Cristiane Decat Bergerot

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1430P Sexual functioning and quality of life in Egyptian premenopausal patients receiving treatment for breast cancer

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Background: The relationship between family-associated factors and the postoperative prognosis is unknown in patients with non-small cell lung cancer (NSCLC). We hypothesized that family-associated support was associated with postoperative prognosis via nutritional pathway. The aim of this study is to elucidate the relationship between family-associated factors and postoperative prognosis in patients with NSCLC.

Methods: We selected 195 patients with NSCLC who underwent curative surgery between 2005 and 2010 whose computed tomography images within 1 month preoperatively and after 1 year postoperatively were available. The nutritional indices such as body mass index, Karnofsky performance index (KPN), oncologic nutrition index (ONI), modified Glasgow prognostic score (mGPS), and skeletal muscle area (SMA) were used to estimate the change in nutritional condition after 1 year postoperatively. Paravertebral muscle area was used to analyze the Shive’s index.

Results: One hundred and forty-four patients (73.8%) had both children and a partner. Twenty-seven (13.8%) only had children and 14 (7.2%) only had a partner. Childless patients showed a significantly shorter overall survival (OS) and disease-free survival (DFS) than those with children (p = 0.002, p = 0.001, p < 0.01 and p = 0.028, respectively). Childless patients with a partner showed a particularly shorter OS and DFS than those with children (p = 0.001 and p = 0.001, respectively). Childless patients with a partner showed significant postoperative exacerbation of PNI, CONUT, mGPS and SMA were found to be significantly correlated with childless patients compared with those with children (p = 0.002, p = 0.001, p < 0.01 and p = 0.028, respectively). Childless patients with a partner showed a particularly shorter OS and DFS than those with children (p = 0.037, p < 0.01, p < 0.01, and p = 0.039, respectively).

Conclusions: The patients without any children had a significantly poorer postoperative prognosis than those with children. The childless partner-present patients showed a significantly shorter overall survival (OS) and disease-free survival (DFS) than those with children (p = 0.002, p = 0.001, p < 0.01 and p = 0.028, respectively). Childless patients treated within PUB show worse outcomes than PRI counterparts, and they are at higher risk for multiple physical, psychological, and financial morbidity. Earlier identification of biopsychosocial screening with appropriate supportive care may improve their QOL.

Legal entity responsible for the study: Shinkichi Takamori

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1431P Primary results of a study to evaluate a decision aid for women offered neoadjuvant systemic therapy for breast cancer

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Background: Women diagnosed with large or highly proliferative operable breast cancer may be offered neoadjuvant systemic therapy (NAST) for reasons including down-staging, prognostication or expanding surgical options. We aimed to systematically develop, and evaluate a DA for women who had been offered NAST.

Methods: Eligible women who were considered candidates for NAST, from four Australian recruiting centres were enrolled in a single arm longitudinal study. Participants completed online questionnaires prior to accessing the DA, and on three occasions post-DA. Primary outcomes were feasibility of use, and acceptability to patients and clinicians. Secondary outcomes were patient reported measures relevant to patient decision-making.

Results: Seventy-nine women were offered study participation and 59 enrolled. Patients were typically well educated, married, had health insurance and were information seekers (mean information needs: 7.5/10; SD 1.8). 39/79 (49.7%) patients who were offered study participation accessed the DA and 49 (79.7%) of those 59 participants reported having read it. 41/51 (80.4%) participants who completed the post-DA assessment reported that the DA helped them with their decision about NAST. 31/59 (56%) participants elected to receive NAST; 16/18 (88.9%) investigators would continue to use the DA in routine practice. Post-DA, decisional conflict decreased significantly across all subscales (p < 0.01); anxiety and distress decreased significantly; 86.3% achieved at least as much decisional control as they desired; a high level of knowledge was demonstrated; and 39/51 (76.5%) patients had a high (24+) Satisfaction with Decision score (mean 25.5, SD 3.6). 84.4% reported that they shared responsibility for the decision about NAST. Investigators reported that the DA was able to be integrated into patient care.

Conclusions: Study primary outcomes were positive, showing the DA was feasible and acceptable to patients and clinicians. Improvements in decision-related outcomes were demonstrated, and the DA could be included in routine workflow. This DA can be implemented into routine clinical practice for women with operable breast cancer who are candidates for NAST.

Clinical trial identification: Registration: Australia and New Zealand Clinical Trials Registry (www.anzctr.org.au): ACTRN12614001267640

Legal entity responsible for the study: Australia and New Zealand Breast Cancer Trials Group

Funding: HCF Research Foundation Australia and New Zealand Breast Cancer Trials Group

Disclosure: All authors have declared no conflicts of interest.
Burnout syndrome: What impact on clinical research?

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Background: Burnout is a job-related psychological syndrome causing depersonalization, emotional exhaustion and lack of personal accomplishment. Albeit studies mainly focus on professionals who have a direct contact with patients, physicians and nurses, little is known about burnout among other professionals employed in clinical research, that requires stressful efforts to maintain quality standards. We decided to evaluate perceived and actual burnout levels experienced by professionals who are at the “bottleneck” of research. Clinical Research Coordinators (CRCs).

Methods: The Gruppo Italiano Data Manager spread an anonymous questionnaire among about 130 CRCs. The survey consisted of 8 items on workload and perceived stress levels and a specific burnout test developed by a group of Italian psychologists.

Results: The survey was completed by 36% of subjects. On average, interviewed CRCs work 42 hours/week and follow 25 studies; 89% feel stressed and 64% believe that this affects negatively the quality of their work. Moreover, 57% of CRCs declare that this condition may soon cause a job change. The major sources of stress are: contract type (43%); workload (17%); lack of skills recognition (11%). Interestingly, the factor that most frequently has been identified among the first 3 causes of stress is the contract type (81%), followed by lack of skills recognition (32%). Based on the psychological test, the average stress level of the sample is 68 points out of overall 225; the highest levels pertain the emotional (average: 17.0/45) and physical spheres (16.3/45), while the social area is the least affected (9.7/45). Stress levels show only a very weak correlation with workload (Pearson coefficient = 0.062) and hours worked (0.095).

Conclusions: Albeit almost all CRCs perceive high levels of stress, psychological testing shows a medium-low degree of burnout. An explanation could be that CRCs are settled into distressing work conditions, so this no longer results in burnout. Burnout was substantially uncorrelated to quantitative estimates of workload, rather depending on other, qualitative, factors, such as lack of skills recognition and contractual instability. Lastly, our data suggest that current workload evaluation methods, mainly based on the number of followed studies, are no longer appropriate.

Legal entity responsible for the study: Gruppo Italiano Data Manager (GIDM)
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Effectiveness of the HuCare Quality Improvement Strategy on health-related quality of life in patients with cancer: Study protocol of a stepped wedge cluster randomized controlled trial (HuCare2 study)

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Background: Our group previously demonstrated the feasibility of the HuCare Quality Improvement Strategy – HQIS, aimed at integrating into practice 6 psychosocial interventions recommended by international guidelines. This trial will assess whether the introduction of the strategy in oncology wards improves patient Health-related quality of life (HRQoL).

Trial design: Multicenter, incomplete stepped-wedge cluster randomized controlled trial, conducted in three clusters of 5 centers each, in three equally spaced time epochs. The study also includes an initial epoch where none of the centers is exposed to the intervention, and a final epoch when all centers will have implemented the strategy. The intervention is applied at a cluster level, and assessed at an individual level with cross-sectional model. 720 patients who received a cancer diagnosis in the previous 2 months and about to start medical treatment will be enrolled. Primary aim is to evaluate the effectiveness of the HQIS vs standard care in terms of improvement of at least one of two domains (emotional and social functions) of HRQoL using the EORTC QLQ-C30 questionnaire, at baseline and at 3 months. This outcome was chosen because cancer patients generally exhibit low HRQoL, particularly at certain stages of care, and because it allows to assess the strategy’s impact as perceived by patients themselves. The HQIS comprises three phases: 1) clinician training - to improve communication-relational skills and instruct on the project; 2) center support – 4 on site visits by experts of the project team, aimed to boost motivation, help with context analysis and identification of solutions; 3) implementation of EBM recommendations at the center.

Clinical trial identification: NCT03008993

Legal entity responsible for the study: Italian Association of Medical Oncology (AIOM)
Funding: Association of Medical Oncology (AIOM); MEDeA (non-profit volunteer association)
Disclosure: All authors have declared no conflicts of interest.
Background: Each year, over 3 million Europeans are diagnosed with cancer, and over 1 million Europeans die from the disease. With a growing and ageing population, action is urgently needed to address this major global health and societal concern. Action is needed to help policy-makers understand how they can improve access to innovative cancer care and to ensure that the patient organisations that form the membership of the European Cancer Patient Coalition.

Methods: The European Cancer Patient Coalition developed the white paper over a one-year period, in collaboration with Interel Public Affairs, oncology experts, and the patient organisations that form the membership of the European Cancer Patient Coalition.

Results: The “Value of Innovation in Oncology” white paper presented the position of the European Cancer Patient Coalition on innovation in oncology, and offered recommendations to help reduce variations in access to innovative cancer care and treatment for Europeans diagnosed with cancer.

Results: We identified 137 studies; 109 (80%) of which were RCTs. Those led to the approval of 63 individual drugs for 118 licensed indications. Among the 105 RCTs for which the ESMO-MCBS could be applied, 7 (6%) were in the neo/adjuvant setting and 98 (94%) in the palliative setting. Only 46 (44%) met the ESMO-MCBS clinically meaningful benefit threshold (100% of neo/adjuvant trials and 41% of palliative trials). In multivariable analysis of palliative therapy trials, meaningful ESMO-MCBS grades were associated with phase III trials (compared to phase II; OR 38.45, P = 0.004), those with overall survival as their primary endpoint (compared to intermediate endpoints; OR 8.28, P = 0.001) and trials of targeted drugs with companion diagnostics (OR 11.62, P < 0.001). Over time, there has been an increase in the number of trials meeting the ESMO-MCBS threshold (33% in 2006 vs. 67% in 2016, P for trend = 0.04). There was an insufficient number of neo/adjuvant studies to perform statistical analysis.

Conclusions: In patients with advanced solid tumours, fewer than half of RCTs supporting FDA approval meet the threshold for clinically meaningful benefit using validated scales.

Legal entity responsible for the study: None

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1441PD Magnitude of clinical benefit of randomized controlled trials supporting US Food and Drug Administration approval of drugs for solid tumours

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Background: The European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) is a validated and reproducible tool to assess the magnitude of clinical benefit from drugs for solid tumours. Here, we evaluate characteristics and outcomes of clinical trials supporting approval by the FDA and their association with ESMO-MCBS.

Methods: We searched the DrugInfo/PEDAS website for applications of anticancer drugs from January 2006 to December 2016. Drug labels and reports of registration trials were reviewed and study characteristics, efficacy, toxicity and quality of life outcomes as well as regulatory pathways were collected. For randomized controlled trials (RCTs) ESMO-MCBS grades were applied. Meaningful clinical benefit was defined as a grade of A or B for trials of neo/adjuvant intent and 4 or 5 for those of palliative intent. Comparisons between groups were assessed using Logistic regression and the Mann Whitney U test.

Results: We identified 137 studies; 109 (80%) of which were RCTs. Those led to the approval of 63 individual drugs for 118 licensed indications. Among the 105 RCTs for which the ESMO-MCBS could be applied, 7 (6%) were in the neo/adjuvant setting and 98 (94%) in the palliative setting. Only 46 (44%) met the ESMO-MCBS clinically meaningful benefit threshold (100% of neo/adjuvant trials and 41% of palliative trials). In multivariable analysis of palliative therapy trials, meaningful ESMO-MCBS grades were associated with phase III trials (compared to phase II; OR 38.45, P = 0.004), those with overall survival as their primary endpoint (compared to intermediate endpoints; OR 8.28, P = 0.001) and trials of targeted drugs with companion diagnostics (OR 11.62, P < 0.001). Over time, there has been an increase in the number of trials meeting the ESMO-MCBS threshold (33% in 2006 vs. 67% in 2016, P for trend = 0.04). There was an insufficient number of neo/adjuvant studies to perform statistical analysis.

Conclusions: In patients with advanced solid tumours, fewer than half of RCTs supporting FDA approval meet the threshold for clinically meaningful benefit using validated scales.

Legal entity responsible for the study: None

Funding: None

Disclosure: All authors have declared no conflicts of interest.
1443PD  Analysis of compliance factors for colorectal cancer screening using a Bayesian network

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Background: Compared to standard explanatory analyses based on multivariate regressions, Bayesian network analyses enable multiple hypotheses and clear graphical representations of complex interactions. They provide visual descriptions of causal pathways to distinguish between direct and indirect factors. We compared multivariate regression and a Bayesian network to assess factors associated with colorectal cancer (CRC) screening. Methods: The 5th French observational survey, EDIFICE 5, was conducted (Nov 22-Dec 7, 2016) by phone interviews of a representative sample of 1501 individuals (age, 30-73 y). The present analysis focuses on 1299 individuals with no history of cancer (50-74 y). Bayesian analysis was performed with the bilateral R Package. Parameters of the Bayesian analysis were based on the literature and our own data (logistic regression). "Blacklist/whitelist" type restrictions were used to reset current understanding of the correlations between variables. We also analyzed the network topology. Results: In our sample, 36% (N = 469) declared never having undergone CRC screening (colonoscopy, fecal occult blood test) in their lifetime. The Bayesian model revealed 5 direct correlating factors: age, smoking status, social vulnerability, psychological re- habilitation, and fear of the disease. Following the logic of the Bayesian network, two nodes were separated (level of education and self-perception of own risk of CRC) and gender, temporal perspective, confidence in their physicians and the fear of the disease. Multiple regression analysis identified PRST (OR = 0.84, 95% CI 0.80-0.88, P < 0.01) and fear of the disease (OR = 0.90, 95% CI 0.86-0.96, P < 0.01) as the two main criteria. Conclusions: We showed that Bayesian network analysis provides a novel representation of factors associated with CRC screening, and may explain why interventions focusing on indirect factors might be ineffective if the next step of the causal pathway remains unchanged. We suggest that Bayesian networks should be used more often to focusing on indirect factors might be ineffective if the next step of the causal pathway remains unchanged. We suggest that Bayesian networks should be used more often to

1444PD  Cancer Clinical Practice Guidelines: Evaluation of ESMO, NICE and SIGN diversity

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Background: This research study is on the critical appraisal of the impact of cited search evidence underpinning the development of cancer clinical practice guidelines (CCPGs) by the professional bodies of the European Society for Medical Oncology (ESMO), the National Institute for Health and Care Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN). Methods: A total of 101 CCPGs were identified from ESMO, NICE and SIGN websites. Their 9,486 cited references were downloaded from the Web of Science, the Cochrane Library, EMBASE and PsycINFO. Studies, King's College London, London, UK

Results: ESMO CCPGs mostly cited research from Western Europe while the NICE and SIGN ones from the UK, Canada, Australia and Scandinavian countries. The ESMO CCPGs cited more recent and basic research (e.g. genetics), in comparison to NICE and SIGN CCPGs where older and more clinical research (e.g. drugs treatment) papers were referenced. This chronological difference in the evidence-base is also in line with that ESMO has a shorter gap between the publication of the research and its citation on the CCPGs. It was demonstrated that ESMO CCPGs report more chemotherapy research while the NICE and SIGN more surgery, with the results being statistically significant. Also, breast cancer research was explored individually across the 13 cancer sites. Their 9,486 cited references were downloaded from the Web of Science, EMBASE and PsycINFO. Background: Studies, King's College London, London, UK

Conclusions: This study showed that ESMO, NICE & SIGN differ in their evidence-base. Healthcare professionals should be aware of this heterogeneity in effective decision-making of tailored-treatments to patients irrespective of geographic location across Europe. Considered the potential of the United Kingdom entering the European Union, a closer collaboration between these professional bodies can lead to the use of more evidence-based, relevant and updated clinical practice guidelines. Legal entity responsible for the study: Elena Pallari, King’s College London Funding: None Disclosure: All authors have declared no conflicts of interest.

1445PD  Cancer screening compliance factors in older patients

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Background: Whereas older patients represent the major part of new cancer cases, their underrepresentation in clinical trials leads to weak external validity. The main objective was to assess the proportions of older patients for whom there is an ongoing clinical trial available, eligible to at least one trial, invited to participate and finally included. Secondary objective was to investigate associated factors. Methods: The SAGE multicenter prospective cohort study settled up in 7 centers in Paris Area between 2013 and 2016. All patients aged 65 years or more with a colorectal cancer were included. The endpoints were 1) the presence of at least one ongoing clinical trial available regarding stage and tumor location 2) the patient’s eligibility 3) invitation and 4) inclusion. Results: 577 patients (mean age: 75.6 years ± 7.1; 56% of men; 74% of colon tumor; 40.9% with metastasis) were included; 37 trials were ongoing (9 trials in median per center; academic sponsors: 62.2%; phaseI/II: 59.5%; chemotherapy: 75.7%). Overall, 12.3% of patients were included in a trial (65.9 yrs class: 19.1%; 70-75 yrs: 14.9%; 75- 79 yrs: 12.8%; 80 yrs or more: 2.6%); p < 0.001). 18% (103/577) had none available trial for his/her stage and tumor location; among patients with available trial, 75% (347- 577) were non-eligible; from the remaining, 34% (43/127) were not invited; from the remaining, 19% (17/88) refused to participate. Non-eligibility was, by order of frequency, related to tumor characteristics (33%), requested para-clinical exams (19%), history of anti-cancer treatment (15%), comorbidities (13.5%), functional status (10%) and age (5%). Among eligible patients, increased age, Perormans Status and decreased Body Mass Index were independently associated with non-invitation (Table). Among patients invited to participate, patient’s refusal was not associated with age.

Table: 1445P Factors independently associated with non-invitation to clinical trials in older eligible patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Adjusted Odds Ratio (95%CI)</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Age, years 65-60</td>
<td>Reference (1.00)</td>
<td>0.01</td>
</tr>
<tr>
<td>70-75</td>
<td>0.26 (0.07-0.90)</td>
<td>0.01</td>
</tr>
<tr>
<td>75-80</td>
<td>0.23 (0.06-0.96)</td>
<td>0.02</td>
</tr>
<tr>
<td>&gt; 80</td>
<td>0.05 (0.01-0.29)</td>
<td>0.03</td>
</tr>
<tr>
<td>PS 0</td>
<td>Reference (1.00)</td>
<td>0.02</td>
</tr>
<tr>
<td>1</td>
<td>0.19 (0.09-0.37)</td>
<td>0.04</td>
</tr>
<tr>
<td>&gt; 2</td>
<td>0.50 (0.29-0.75)</td>
<td>0.09</td>
</tr>
<tr>
<td>Body Mass Index, kg/m²</td>
<td>21-24.9</td>
<td>Reference (1.00)</td>
</tr>
<tr>
<td>&lt; 21</td>
<td>0.25 (0.07-0.90)</td>
<td>0.76</td>
</tr>
<tr>
<td>≥ 25</td>
<td>0.76 (0.24-2.42)</td>
<td></td>
</tr>
</tbody>
</table>

*Hierarchical multivariate logistic regression with the patient at the level 1 and the center at the level 2 and adjustment for all variables listed in the table, the number of trials in the center and the number of chemotherapy trials.
Risk of second primary cancers and competing mortality in survivors of adult-onset cancer: changing pattern over three decades

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Background: Survivors of first adult-onset cancers are at risk of developing second primary cancers (SPCs) and are at risk of death from their subsequent cancers and other competing causes. Here we investigated patterns of incident SPC risk and cause-specific mortality in survivors of adult-onset cancer during the past three decades.

Methods: Data were extracted from the population-based Tasmanian Cancer Registry in Australia. Patients diagnosed with a first primary cancer between 1980 and 2009 were followed for incident SPCs to December 31, 2013 and for deaths to December 31, 2014. SPC risks were quantified by using standardized incidence ratios (SIRs). Trends in SPC risk over time were assessed in multivariable Poisson models. The cumulative incidence and subdistribution hazard ratios (SHR) of cause-specific deaths were estimated using competing risk models.

Results: 5,339 SPCs were observed from 51,802 cancer survivors. The SIRs for any SPC increased from 0.98 with a first cancer diagnosis in 1980-1984 to 1.12 in 2005-2009. The increase in SIRs was significant in multivariable Poisson models (P < 0.001). Deaths were most frequent in 1994-1998 (59.8% of 57,288 patients. The cumulative incidence of death due to first primary cancer gradually increased from 12% for a first cancer diagnosis in 1980-1984 to 30.7% in 2005-2009. However, the 5-year cumulative incidence of deaths due to subsequent cancers varied across periods of first cancer diagnosis, with an increase from 1.0% in 1980-1984 to 1.7% in 1995-1999, and a decrease to 1.4% in 2005-2009. The SHR of deaths due to first primary cancer gradually decreased over time to 0.86 (95% CI: 0.76-0.98) in 2005-2009. The risk of death from first primary cancer decreased after 80 years.

Conclusions: The risk of SPC has increased in Tasmania over the last three decades. While the risk of death due to first primary cancer decreased over time, the risk of death due to subsequent cancers did not. The increased risk of deaths from subsequent cancers might be an outcome of overdiagnosis of first primary cancer in the 1990s.

Legal entity responsible for the study: Memere Institute for Medical Research, University of Tasmania

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Effect of rural residence (RD) and distance travel to the cancer center (DTC) on neoadjuvant chemoradiation (NCRT) in localized rectal cancer

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Background: Neoadjuvant chemoradiation therapy (NCRT) has been associated with a lower rate of local recurrence and represents an accepted standard of care. Yet, access to treatment or decisions about treatment can be affected by contextual factors such as rural residence (RD) and distance travel to cancer center (DTC). In the current study, we evaluated the association between RD and DTC and NCRT.

Methods: A cohort of patients diagnosed with localized rectal cancer during 2009-2013 in the province of Saskatchewan was studied. The logistic regression analyses were performed to assess relationship between RD and DTC and lack of NCRT.

Results: A total of 279 patients were identified with median age of 66 years (IQR: 59-76) and M:F of 1.18 (33.6%) had a major comorbid illness. 183 (65%) were rural resident. The median DTC was 141 km (IQR: 7-235). Of 279 patients, 116 (41%) were referred for NCRT, 161 (58%) underwent upfront surgery, and 2 declined surgery. The mean DTC for group treated with NCRT was 111.5 ± 122.5km compared with 169.0 ± 270.6km if they did not receive NCRT (p = 0.01). Of urban resident, 52/96 (54%) were referred for NCRT compared with 64/183 (35%) of rural resident (p = 0.002). After excluding 33 (12%) patients who had clinical stage I disease and underwent upfront surgery, a univariate regression analysis revealed that both DTC (OR 1.92, 95% CI: 1.15-3.20) and RD (OR 2.51, 95% CI: 1.46-4.32) were significantly correlated with lack of NCRT. On multivariate analysis following relationships were noted with lack of NCRT. Age ≥ 70 years (OR 1.45, 95% CI: 0.84-2.45), comorbid illness (OR 1.52, 0.86-2.67), ECOG performance status of > 1 (OR 1.25, 0.49-3.17), DTC (OR 1.07, 0.51-2.25), and RD (OR 2.56, 1.17-5.07).

Conclusions: Our results revealed that RD but not DTC is associated with a lower rate of NCRT in patients with localized rectal cancer. Future studies are required to explore the underlying cause of differential referral.

Legal entity responsible for the study: Saskatchewan Cancer Agency

Funding: None

Disclosure: All authors have declared no conflicts of interest.

European survey of 907 people with cancer about the importance of nutrition

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Background: Nutritional and metabolic disorders are highly prevalent among cancer patients. We aimed to analyse the dimension of nutritional alterations among cancer patients and survivors in Europe by using a structured questionnaire encompassing the perspectives of patients and their physicians on nutritional issues.

Methods: A structured questionnaire was designed to analyse the importance of nutrition for people with cancer. The questionnaire was subdivided in specific areas of interest, such as the presence of feeding problems, perception of nutrition importance, role of food supplements, and their view of their physician’s approach to nutrition. All cancer patients and survivors were eligible to answer the questionnaire, except for people diagnosed with brain and breast cancer. The study was conducted by the European Cancer Patient Coalition (ECPC), Sapienza University of Rome, and Healthcare International. ECPC ensured the dissemination of questionnaire to its Members in 10 countries, who translated and disseminated the questionnaire.

Disclosure: None

Funding: None

All authors have declared no conflicts of interest.

References:

1. Division of Medical Oncology and Hematology, Princess Margaret Cancer Center, presented quantitative data. The median time between lay media reporting and scientific reporting with an increasing trend over time (p < .001). In 49 cases (27%) reporting in the lay media occurred before scientific reporting. We identified 93 (52%) reports in the lay media (66% of positive trials and 38% of negative trials). In 49 cases (27%) reporting in the lay media occurred before scientific reporting. We identified 93 (52%) reports in the lay media (66% of positive trials and 38% of negative trials).

Conclusion: Inclusion of older cancer patients decreased dramatically after 80 years. Moreover, one-third are non-invited to participate and one-fifth refused. Inclusion of older cancer patients decreased dramatically after 80 years. Moreover, one-third are non-invited to participate and one-fifth refused. Inclusion of older cancer patients decreased dramatically after 80 years. Moreover, one-third are non-invited to participate and one-fifth refused.
Results: The survey was answered by 907 cancer patients and survivors. 59.2% (n = 537) of respondents were diagnosed with cancer less than 3 years ago, and 46.2% (n = 419) were treated for cancer for 1 year or less (46.2%; n = 419). 82.4% of respondents (n = 689) believed it was important to maintain physical activity during cancer treatment, although only 53.8% (n = 450) of the respondents reported that their physicians advised them to do so. 72.9% (n = 603) of the respondents didn’t know the meaning of the term “ cachexia”, and 92.4% (n = 764) did not receive any information about cachexia from their health professionals. 69.7% (n = 580) of respondents reported that they lost weight after the cancer diagnosis, and for 36.7% (n = 309) of respondents this loss was moderate to severe.

Conclusions: Most people with cancer surveyed reported that they would like to receive more information about how to improve their nutrition during and after treatment. There is a need to empower individual patients and patient associations by producing more information on cancer patients’ nutritional needs. Such information material should be produced by patients in close collaboration with medical oncologists and other healthcare professionals.

Legal entity responsible for the study: European Cancer Patient Coalition.Funding: Baxter and Helsinn. Disclosure: All authors have declared no conflicts of interest.

1452P Risk of malignant mesothelioma in Spain from environmental asbestos exposure

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Background: The link between malignant mesothelioma (MM), and asbestos exposure (AE), is very high. AE may have occupational or environmental non-occupational source. The highest levels of AE occur in the workplace and mainly affect men. However, environmental AE, affect men and women equally. As the occupational AE prevails over the environmental non-occupational, a sex-ratio < 2 alert of possible environmental AE. The objective of this study is to evaluate the spatio-temporal distribution of the sex-ratio, in order to identify those areas with possibly higher environmental AE.

Methods: We conducted an analysis of the 6,143,124 deaths in Spain during the period 2000–2015, looking for those deaths caused by MM. Information regarding sex, year of death, age at death, province, and cause of death (ICD-10) was extracted from the deceased registry of the National Institute of Statistics. We calculated the sex-ratio between the deceased by MM according to its distribution by provinces and years, and the ratio of mortality rates adjusted for age (European standard population). We also obtained the proportion of MM among the total deceased (MM per 10,000 deaths).

Results: MM deaths were 5,345. Men 4,025 and women 1,329 (sex-ratio: 3.31). During the 2000-2015 period the sex-ratio remained relatively stable, ranging from 2.21 in 2007 to 4.31 in 2005. In the years 2000 and 2015 the sex-ratio was 3.34 and 3.07, respectively. Likewise, in the years 2008/2015 the men/women age-adjusted rates was 2.83 and 3.93, respectively. The variations by provinces were more pronounced. The lowest sex-ratios (1.5) corresponded to the 140 deaths of Navarra and the highest (12.67), to the 41 deaths of Vitoria. Other low sex-ratio values were detected for Almeria (2.07), Donostia (2.02), Huesca (2) and Taragona (1.97). Among those provinces with a possible higher environmental AE risk (sex-ratio equal to or < 2.07), Donostia and Navarra have a high MM mortality (more than 13/10,000 deaths), but the other have a low or medium mortality.

Conclusions: The high provincial variability in Spain of the proportion of women who died of MM, makes necessary the carry out of new research focused in the provinces detected as with a possible greater risk of environmental asbestos exposure in the general population.

Legal entity responsible for the study: Jose Miguel Sanz-Anquela, Junior Smith Torres-Roman.

Funding: None.

Disclosure: J.M. Sanz-Anquela: Occasionally has served as a consultant to the court, always at the request of plaintiff asbestos victims. All other authors have declared no conflicts of interest.

1453P Tobacco exposure and adverse pathological features in oral cancer: Does age impact survival?

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Background: The role of tobacco in oral cancer is well established, however there is a wide variation in the incidence of tobacco - related oral cancer in the literature, ranging between 70-90%. Our data shows that only half of the patients with oral cancer have any history of tobacco exposure (smoking, chewing or others). Younger patients with oral cancer (<30 years) are being shown to be a distinct subset of patients, with more aggressive disease, possibly due to an underlying immunological basis. No previous literature has shown if the effect of tobacco exposure is similar in all age groups.

Table: 1451P

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Does age impact survival?
Methods: From a prospectively maintained database of patients treated for oral cancer in our institution, we extracted details for 643 patients of oral cavity squamous cell carcinoma. We divided these patients into four groups, younger patients (<55 years) with or without tobacco exposure and older patients (≥55 years) with or without tobacco exposure and compared the effect of any tobacco exposure on prognostically relevant variables (like diameter, depth of invasion, extranodal extension). We also compared the progression free survival (PFS) and overall survival (OS) between those with and without tobacco exposure in each age group separately.

Results: The percentage of those with tobacco exposure was comparable in both age groups. Tobacco exposure correlated with tumour thickness (p = 0.001), perineural invasion (p = 0.002), lymphovascular invasion (p = 0.004) and local recurrence (p = 0.006) in the younger patients but not in the older patients. In younger patients, those with tobacco exposure also had a positive trend for poorer differentiation (p = 0.07) and extranodal extension (p = 0.06). Patients <55 years who had a history of tobacco exposure, had a significantly worse PFS and OS (p = 0.03). In patients ≥55 years, the PFS and OS between the cohorts with and without tobacco exposure was comparable (p = 0.10).

Conclusions: Younger patients with exposure to tobacco have worse clinical outcome, possibly as a result of adverse pathological features like perineural invasion and lymphovascular invasion. Whether this relationship is due to an underlying immune mechanism requires further study. Younger tobacco users with oral cancer are more likely to have a poor prognosis.

Legal entity responsible for the study: Amrita Institute of Medical Sciences, Kochi, India

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1455P Initiation of systemic anti-cancer treatment in the inpatient setting in a tertiary hospital in London

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Background: The landscape of adult medical oncology care has shifted across the past three decades from the hospital to the outpatient setting, reflecting factors such as patient preference, technological advancements in the delivery of therapeutics, and cost-effectiveness. There are no recent guidelines to indicate when systemic treatment should be initiated as an inpatient. This clearly presents difficulties, particularly since initiation of treatment is often dependent on the patient's clinical presentation at the time of admission.

Methods: We retrospectively generated data of patients at the Royal Free Hospital commencing cycle 1 of chemotherapy as an inpatient, with a particular focus on 30-day mortality, overall survival, performance status recorded prior to initiation, treatment dose and line of therapy. Data was collected over a period of 24 months from January 2015 to December 2016.

Results: We identified 34 patients across a range of tumour types and with varying performance status who fulfilled our criteria. The median age of patients treated was 54.5 years. Of these, the 76% (26/34) were administered full dose therapy, with 17.6% given a 25% dose reduction, and 5.8% given with a 50% dose reduction. Of the 34 cases, 76% (26/34) were first line therapy. The treatment intent in all cases was palliative, except one case where the intent was neoadjuvant. There was a positive correlation between performance status, full-dose therapy, and first line therapy with survival.

The outcomes of inpatients were significantly worse than outpatients. 7 of 34 in our cohort died with 30 days (25.8%), while only 3.8% of them were alive at 6 months. This is compared to the overall 30-day mortality rate of our department at 2.9%.

Conclusions: 1) Inpatients commenced on systemic treatment are associated with poorer overall survival compared with outpatients. 2) We would suggest adherence to the new `2016 UK QOIN: Optimising Palliative Chemotherapy Decision Making', which recommends a discussion within the MDT when chemotherapy is commenced or continued when PS is greater or equal to 2, decisions regarding commencement of 2nd line treatment or beyond are required, when there is outright progression through the first cycle of chemotherapy.

Legal entity responsible for the study: Oncology Department, Royal Free Hospital, London

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1456P Young-age onset colorectal cancer: Analysis of incidence, clinical features and outcomes

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Background: Recent studies suggest an increase in the incidence of colorectal cancer (CRC) in young-age patients. Data concerning clinical behavior, pathologic findings and prognosis are still poorly understood for this age group. The aim of this study is to analyze clinical features and survival of the young-onset CRC population in Brazil.

Methods: We retrospectively reviewed records of 5,806 patients diagnosed with CRC between January/2011 and November/2016 in Instituto do Câncer do Estado de São Paulo and identified 781 patients aged 50 years or younger. Kaplan-Meier method was used to estimate overall survival (OS) and univariate analysis were carried out to identify factors associated with OS.

Results: We found an absolute increase in the incidence of CRC in patients < 50 years by 1.88% to 2.13% annually (2011-2012: 11.6%, 2013-2014: 13.3%, 2015-2016: 15.7%). CRC incidence increased with a relative increase of 33.3% between 2011 and 2016. Median age was 42 years (17-49). 57.4% were female and 20.9% reported family history (FH) of CRC. Mismatch repair (MMR) protein immunohistochemical analysis were performed in 466 patients and 78 (16.7%) had MMR deficient CRC. Left-sided tumors were more frequent (left colon 8.2%, sigmoid 33.7% and rectum 31.5%), whereas the incidence of right-sided tumors was 19.4%. Almost all of patients were symptomatic (93.9%) and abdominal pain (39.6%) and rectal bleeding (28.7%) were common. MMR deficiency was associated with better OS (p = 0.029). The stage distribution was stage I 12.6%, II 25.8%, III 34.1% and IV 37.5%. The median OS of stage IV was 25 months (CI95% 20.7-29.3) and not reached for I-III (p < 0.001). FH of CRC (p = 0.021) and adjuvant chemotherapy (p = 0.001) were independently associated with better OS in stage IV. For stages I-III, wild-type KRAS (p = 0.003), FH of CRC (p = 0.024) and absence of lymphovascular invasion (p < 0.001) were associated with better OS.

Conclusions: In our experience, the incidence of early-onset CRC is increasing. Young patients were more likely to be diagnosed with metastatic disease, left-sided/rectal site and symptoms at presentation. These findings highlight the emerging importance of young-age onset CRC and the need to discuss strategies to early diagnosis.

Legal entity responsible for the study: Instituto do Câncer do Estado de São Paulo

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1457P Improved provision of written information on metastatic spinal cord compression to at-risk cancer patients at a tertiary referral centre

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Background: Metastatic spinal cord compression (MSCC) affects up to 10% of patients with disseminated malignancies, and early diagnosis correlates with improved clinical outcomes. Up to 85% of patients who present with MSCC already have motor deficit by the time of presentation. We investigated our Trust’s compliance with national guidelines on providing at-risk patients with written information on the signs and symptoms of MSCC. Following a period of educational intervention we re-audited our practice.

Methods: All Oncology doctors and Specialist Nurses at the Royal Free Hospital were completed an online survey on their knowledge of national guidelines and their clinical practice. We delivered an educational intervention (including formal teaching and presentation at Departmental meetings, case discussions and providing patient information leaflets to clinicians) and re-audited our practice after 3 months.

Results: There were 29 and 20 respondents to the baseline and repeat surveys respectively. 57% vs 84% reported being moderately or very familiar with the MSCC guidelines; 32% vs 47% reported knowing where the information leaflets were kept; 3% vs 15% reported providing written information on MSCC to at-risk patients at least every month. (baseline and repeat surveys, respectively)

There was a consensus amongst the clinicians that patients with spinal metastases should be considered at “highest risk”, and verbal information about the risks of MSCC was most commonly given to this group. There was a 42% increase in the proportion of respondents who provided written information on the risk of MSCC to patients with spinal metastases (19 vs 61%) following the intervention.

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Conclusions: 1) Provision of written patient information leaflets, formal education sessions and case discussions with clinicians resulted in increased knowledge of guidelines on MSCC at 3 months, and positive changes in clinical practice. 2) There was a significant increase in the provision of written information to the highest risk patient groups (19 to 61%). 3) By increasing patient awareness, we can increase the proportion of early self-presentations and diagnosis. This will lead to prompt intervention and improvement of neurological outcomes.

Legal entity responsible for the study: Oncology Department, Royal Free Hospital

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1458P Impact of mastectomy on the social well-being and family dynamics of breast cancer female patients in the Gaza Strip

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Background: The impact of mastectomy on social well-being (SWB) and family dynamics (FD) may involve the individual, social role and perception of the usefulness of social and family support affects. The purpose of the current study is to identify that impact to diagnose and treat it. In Greece, this data collection is managed only in the island Regional Council, Heraklion, Greece, 6Respiratory Medicine, University Hospital of Heraklion, Heraklion, Greece, 5Region of Crete, NHS Foundation Trust

Methods: This was a cross-sectional study in which a total of 173 female patients who had mastectomy in GS hospitals completed a face-to-face questionnaire designed by the researchers; which contains 3 sections including: socio-demographic data, SWB and FD. All measures utilized a five-point Likert-type scale ranging from 1 (worst outcome) to 5 (best outcome). The study was conducted at European Gaza Hospital (n = 60) and Alshifa Hospital (n = 113) in the GS from August 2015 to September 2016. The data was analyzed using SPSS software.

Results: Among 173 female patients, the mean age was 51 years ± 10. About 91% were unemployed, 52% had low income and 77% were of low educational level. The overall SWB score was moderately affected by 44.2% (mean score 2.21 ± 1.33). Seventy percent of patients had a financial impact and decreased home activities. Interestingly, 57.8% claimed that involvement in family activities was not affected after mastectomy. Shockingly, 95.4% of women worried of getting divorced due to their illness. The overall impact on FD is estimated to be 49.2% (mean score 2.46 ± 1.64). Surprisingly, the diagnosis of BC had an impact on sexual performance in 27.1% compared to 19.1% after mastectomy.

Conclusions: Improving patients’ quality of life should be one of the primary goals of BC treatment. Involving patient’s family in the process of medical care may promote their SWB and FD. However, the great fear of divorce found in this study, demonstrates the insecurity of women within the society of Gaza and is possibly an expression of the lack of security in the Gaza-Strip. Assessing and addressing the SWB and FD among BC patients may enhance providing a holistic medical care and further research in the future can help in implementing this.

Legal entity responsible for the study: Faculty of Medicine at the Islamic University of Gaza, Gaza-Strip, Palestine

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1459P Cancer incidence and mortality trends in Crete, Greece during the last two decades (1992-2013): Results from the cancer registry of Crete

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Background: Cancer registration is the systematic collection of data about cancer and tumor diseases and is a valuable tool for understanding what causes cancer and how best to diagnose and treat it. In Greece, this data collection is managed only on the island of Crete, by the Cancer Registry of Crete (CRC). In this study, we present data on the cancer incidence and mortality for all neoplasms in Crete, during 1992-2013. Secondary objectives were to map the longitudinal trends of all MNI and per type.

Methods: Data were obtained from the Cancer Registry of Crete which is the only population-based registry in Greece since 1992 (permanent residents~623,000). Data were coded according to the ICD-10 and included several parameters on demographic, medical history, and lifestyle factors. Age-standardized incidence/mortality of 100,000/year (ASIR, ASMR) were estimated, while Bayesian models were performed to assess any longitudinal variations (a = 0.05).

Results: ASIR and ASMR for all cancers in Crete were 302.8 and 150.5 respectively. Cancer of the lung and bronchus is the most common invasive cancer and cause of cancer mortality in males and females (40.2 new cases/100,000/year and 36.5 deaths/100,000/year). Colorectal cancer accounted for 23.1 new cases/100,000/year and 14.7 deaths/100,000/year, and breast cancer for 28.6 new cases/100,000/year and 11.1 deaths/100,000/year. The invasive neoplasms that presented the greatest statistically significant increasing trends during the past 22 years were: lung and bronchus (in women), colorectal cancer, leukemia (in men) and thyroid cancer (in both sexes).

Conclusions: Although the Cretan cancer rates are still lower than the mean European one, significant increasing trends were identified: indicating the urgency for clinical and public health measures. Since the cancers that account the most in this increase are preventable by smoking cessation, screening, and vaccination. High priority should be given to the development of population-based interventions.

Legal entity responsible for the study: University of Crete

Funding: Region of Crete

Disclosure: All authors have declared no conflicts of interest.

1460P Robotic anticancer drug compounding assist system for the preparation of injectable antineoplastic drugs

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Background: Many antineoplastic drugs are known to be mutagenic or teratogenic. Medical personnel handling antineoplastic drugs are at a high risk of occupational exposure. Therefore, in collaboration with Yaskawa Electric Corporation and Nikka Micron Co., Ltd, we developed the Cancer Drug Compounding Assist System (CDCAS). The CDCAS is an automated robotic system designed to efficiently facilitate the accurate preparation of drugs based on dose. In this study, we evaluated the CDCAS for accuracy, site contamination, and washing performance in the preparation of antineoplastic drugs.

Methods: 5-Fluorouracil (5-FU) 600, 800, or 1200 mg was added to 100 mL of saline; 5 samples of each formulation were prepared. The weight of the mixed drugs prepared using the CDCAS was compared to those prepared by a pharmacist, and the accuracy of each preparation was calculated in terms of percentage relative error. The acceptable variance was set at ± 5%. To test for contamination, cyclophosphamide (800 mg) was continuously added to 50 bags of 100 mL saline solution. Then, 25 locations inside the isolator were identified for measurement. Cyclophosphamide was collected from those sites by using a sampling sheet method. Twenty of those samples revealed adherence of 5-FU (300 mL) to the infusion bag surface. Ozonated water was used to wash 5-FU from the surface of the infusion bags. After the washing process, any 5-FU remaining on the infusion bag surface was recovered via a wiping method.

Results: The average weight error ratio for the CDCAS and the pharmacist was -0.62% and 2.69%, respectively. Contamination of cyclophosphamide was confirmed at eight sites. Pollution of 5-FU was confirmed for two samples, and the removal rate was ≥ 99.9%. 

Conclusions: Our study demonstrated that the CDCAS’s preparation accuracy and cleaning performance are within acceptable limits. Thus, the CDCAS could be used to potentially reduce occupational exposure to antineoplastic drugs.

Legal entity responsible for the study: Satohiro Masuda

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1461P Monitoring of contamination with cytostatics in pharmacies and hospitals in the Czech Republic

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Background: Monitoring of contamination with cytostatics was introduced in practice in the Czech Republic by CYTOC project managed by the pharmacy of Masaryk Memorial Cancer Institute (MMI) in years 2006-2010. The number of prescriptions of cytostatic drugs increased within the Czech Republic from 2000 bags and syringes in 2010 up to 38000 in 2015. So as to set up standards for the protection of healthcare professionals, it is necessary to monitor contamination regularly at all work sites engaged in compounding or administration - both in the pharmacy (Pharm) and at the hospital departments (HD)/stationaries (S). We have introduced the monitoring of cyclophosphamide (CP) and Pt cytostatics (Pt) to routine practice in 2007. In 2015, there was also implemented monitoring of 5-fluorouracil (FU). These drugs belong to the most frequently used cytostatics in MMI (49.0% of compounded units).

Disclosure: All authors have declared no conflicts of interest.

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Disclosure: All authors have declared no conflicts of interest.
Methods: The Alliance for Safe Biologic Medicines (ASBM) conducted regional, 15-minute web-based surveys among biologics prescribers around the world to determine their opinions on biosimilar substitution. Prescribers were asked to rate: (1) the importance of authority to decide the most suitable biologic for their patients, (2) the importance of designating a biologic as “dispense as written” (DAW, or equivalent), (3) the acceptability of biosimilar substitution, and (4) the importance of notification of biosimilar substitution. Results: A total of 1,856 responses were received: 470 (25%) Europe, 427 (23%) Canada, 400 (22%) US, 399 (21%) Latin America, and 160 (8.6%) Australia. Across regions, most prescribers were from the hospital setting, and most had ≥1 years in practice. Between 10% and 25% of prescribers were oncologists (16% Europe, 10% Canada, 16% US, 18% Latin America, and 25% Australia). Across regions, most oncologists (75%) feel that it is critically/very important to have sole decision-making authority regarding the suitability of a biologic, and 71% that it is critically/very important to have DAW authority. Only 6% of oncologists feel that pharmacy-level substitution is totally acceptable; 58% consider switching to a biosimilar unacceptable, and 36% consider switching acceptable provided it has been agreed to in advance. Most (79%) also feel that it is critically/very important to be notified of pharmacy-level substitution. Responses were mostly aligned across regions; however, one notable difference was the relatively low percentage of Australian oncologists (23% vs 58% overall) who feel that substitution is unacceptable. Conclusions: Our survey indicates that most oncologists believe it is important for them to be able to control which biologic—original product vs biosimilar—they prescribe for their patients. This is likely to become increasingly important with the availability of biosimilars used for curative intent.

Legal entity responsible for the study: Alliance for Safe Biologic Medicines

Funding: Amgen and AbbVie

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Feasibility and barriers to optimal oncological treatment in solid organ transplant patients with de novo cancer

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Background: Transplanted patients (tpts) display higher cancer incidence rates compared to general population. Optimal tumor treatment after transplantation remains scarcely described. This study aimed to report oncological therapy feasibility and outcome in tpts with de novo cancers.

Methods: We retrospectively analyzed all consecutive cases of de novo cancer in renal and liver tpts treated in our center. Pts were identified based on systematic research in tpts databases from 2000 to 2016. Pts presenting with non-melanotic cutaneous tumors only were excluded. Clinical features, treatments, toxicity and survival data were collected. Active optimal treatment was assessed by comparing treatment that was actually administered with guidelines.

Results: Among 4637 pts, 209 cases of de novo cancer were identified in 176 (3.8%) pts. Mean age was 52.5 ± 11.3 at transplantation and 59 ± 10.6 at cancer diagnosis; 122 (69%) were men; 96 (35%) were renal tpts and 80 (43%) liver tpts. At cancer diagnosis, performance status (PS) was 0-1 in 89% (n = 142/160). Tumor type was mainly epithelial (79%, n = 156/200); tumor stage was localized in 80% (n = 163/203) and advanced in 20% (n = 42/203). Among pts with initially localized tumors, 13% (n = 22/165) had cancer recurrence. Median overall survivals of pts with localized and advanced cancer were of 166 (95% CI: 103.3-ND) and 8.8 (95% CI: 5.0-47.2) months, respectively. Among pts with localized tumors, 80% (n = 154/196) received optimal treatment. Reasons for non-optimal treatment were comorbidities in 36% (n = 8/22), risks for the transplant in 36% (n = 8/22), and/or toxicity in 36% (n = 8/22). In contrast, at advanced/recurrent stage, only 36% (n = 18/53) of pts received optimal treatment, and 28% (n = 15/53) best supportive care only. Barriers to optimal treatment were comorbidities in 19% (n = 6/32), risks for the transplant in 22% (n = 7/32), toxicities in 19% (n = 6/32), and poor PS in 33% (n = 17/52).

Conclusions: Oncological treatments are feasible in tpts and survival seems similar to general population. Concerns about the risk of toxicity for the transplanted organ and comorbidities were the main reasons for non-optimal treatment. These observations warrant confirmation in a prospective multicenter study.

Legal entity responsible for the study: CHU Henri Mondor
Funding: None
Disclosure: All authors have declared no conflicts of interest.

Generating patient reported outcome norms for an EU cancer population using real world data (FACT-G)

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Background: The main aim of this analysis was to generate population norms from an EU sample of cancer patients for the FACT-G instrument using real world data. Comparisons were made between existing norms based on a US population and the newly developed EU norms.

Methods: Data was collected through the Adelphi Real World Disease-Specific Programmes (DSPs) across breast, gastric, melanoma, non-small cell lung and prostate cancers. Cross sectional surveys were administered to physicians and patients between January 2015 and March 2017, resulting in a total sample of 4899 patients. The US population norms outlined by Brucker et al. (Evaluation & the Health Professions. 2005;28(2):192-211) are commonly used to aid interpretation of FACT-G scores but there are no large sample norms specifically derived for the EU population. Analysis included checking internal reliability of the FACT-G sub-scales in the EU sample and comparisons between the EU and existing US population norms using minimum important differences (MIDs) of 3 points for FACT-G sub-scales and 7 points for total FACT-G score (Yost et al. Evaluation & the Health Professions. 2005;28(2):172-191).

Results: The EU sample had similar population characteristics to the US sample with respect to age, gender and ECOG status but consisted of a wider sample of cancer types (including haematological cancers). Internal consistency was met (α > 0.7) for all sub-scales within the FACT-G for the EU population. Comparisons between the population norms indicate differences in FACT-G scores between the EU and US samples based on MIDs. Differences exceeding MIDs were noted across social well-being (SWB), emotional well-being (EWB), functional well-being (FWB) and overall FACT-G, but not for physical well-being (PWB). Further analysis was undertaken to explore differences by gender.

Conclusions: Differences highlighted between FACT-G scores for the EU and US cancer populations indicate that population norms may be region-specific or specific to cancer type. The resulting EU population norms can be used to aid interpretation of FACT-G scores across a range of cancer types.

Legal entity responsible for the study: Adelphi Real World
Funding: None

Development of a web-based application using machine learning algorithms to facilitate systematic literature reviews

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Background: Systematic review is an important element of medical research but rapid proliferation of published literature presents challenges to manual review. Computer science advances can improve workload by using algorithms to automatically select and extract data from articles. We initiated a systematic review of phase I immunotherapy clinical trials and used natural language processing to aid article screening.

Methods: A literature search was performed across MEDLINE, Embase and CENTRAL in September 2016 using 100 search terms in the categories “immunotherapy” and “phase I clinical trial”. Only English language studies published since 1990 were included. We developed a web-based interface that allowed human reviewers to apply inclusion/exclusion labels based on title and abstract screening. Articles were screened by two independent reviewers who were blinded to results. An article similarity-based algorithm using weighted logistic regression to predict “include” and “exclude” labels is being trained and herein we report interim results.

Results: 28,235 articles were identified from the literature search, 19,800 remained after duplicates and conference abstracts were excluded. 4,034 (21.2%) were screened, of which 532 (13.2%) were labeled “include” by at least one reviewer. 1,944 (10.2%) were screened by two reviewers with concordance of 93.7%. The prediction algorithm was weighted to improve the detection of “include” labels, and achieved 80.6% sensitivity and 78.2% specificity when compared to manual review results. The positive and negative predictive values were 54.4% and 96.6%, respectively.

Conclusions: A machine learning algorithm trained on manual reviews was able to predict systematic review article inclusion with approximately 80% accuracy. Algorithm performance was affected by the low rate of included articles, but irrelevant articles were able to be excluded with high confidence. Further development is ongoing to optimize the algorithm to improve sensitivity. Once optimized, this innovative machine learning process could transform the conduct of systematic reviews.

Legal entity responsible for the study: N/A
Funding: None
Disclosure: All authors have declared no conflicts of interest.

Survival patterns for different types of cancers in the United States (1973-2012)

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Background: Most studies addressing survival patterns focus on 5-years survival data due to difficulties in long-term patients’ follow up. The aim of this study was to explore data on survival making use of the main advantage of SEER (National Cancer Institute Surveillance, Epidemiology, and End Results) program; that is long-term follow up of patients’ records. This enabled reporting 5-years relative survival, 10-years relative
survival, and 20-years relative survival for different types of cancers. Survival trends as a function of time and tumor types were also provided.

**Methods:** SEER's Stat version 8.3.4 was used for data acquisition and analysis, where SEER (18 Regs Nov 2015 Submission) database was used as the data source. Only cases diagnosed between 1973-2012 with malignant behavior, known age, and microscopic confirmation were included. Relative survival was calculated using Ederer II method. Tumors were classified according to ICD-O-3 into either solid malignancies (8000–8553) or hematological malignancies (9590–9599).

**Results:** Cancer cases diagnosed between 1973 and 2012 showed a 5-years relative survival of 64.6% (CI: 64.5%-64.6%), a 10-year relative survival of 58.7% (CI: 58.6%-58.7%), and a 20-years relative survival of 51.4% (CI:51.3%-51.5%). All of these percentages were much higher with solid malignancies than hematological ones (Table). Long-term follow up data were suggestive of 20-years relative survival of 51.4% for all cancers. Data were also suggestive of improved relative survival over time. Unexpectedly, hematological malignancies, despite most of them being thought of as incurable ones, appeared to have lower relative survival than solid tumors.

**Conclusions:** Long-term follow up data were suggestive of 20-years relative survival of 51.4% for all cancers. Data were also suggestive of improved relative survival over time. Unexpectedly, hematological malignancies, despite most of them being thought of as incurable ones, appeared to have lower relative survival than solid tumors.

**Legal entity responsible for the study:** Mohamed Alaa Gouda

**Funding:** None

**Disclosure:** All authors have declared no conflicts of interest.

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**Table: 1469P showing relative survival data as a function of time and tumor type**

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<td>36.9%</td>
<td>44.4%</td>
<td>54.1%</td>
<td>51.4%</td>
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<tr>
<td><strong>Solid Malignancies</strong></td>
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<tr>
<td>5-Year RS</td>
<td>51.8%</td>
<td>58.7%</td>
<td>66.6%</td>
<td>69.2%</td>
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<tr>
<td>10-Year RS</td>
<td>44.8%</td>
<td>52.4%</td>
<td>61.8%</td>
<td>64.4%</td>
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<tr>
<td>20-Year RS</td>
<td>38.3%</td>
<td>46%</td>
<td>55.6%</td>
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<td>52.7%</td>
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<tr>
<td><strong>Hematological Malignancies</strong></td>
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<tr>
<td>5-Year RS</td>
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<td>48.4%</td>
<td>56.2%</td>
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<td>58.1%</td>
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<tr>
<td>10-Year RS</td>
<td>30.9%</td>
<td>37.5%</td>
<td>47.5%</td>
<td>56.6%</td>
<td>48%</td>
</tr>
<tr>
<td>20-Year RS</td>
<td>22.7%</td>
<td>29.4%</td>
<td>38.6%</td>
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<td>37.9%</td>
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**Results:** 1,090 pts completed the questionnaire (386 (35.6%) men and 697(64.4%) women). Median age was 60 years (IQR 50-69); 311 (29.5%) had previously been offered a CCT and 303 pts had participated. Factors most frequently ranked as important regarding decisions about CCT participation included; chance to advance research (n = 846, 81.0%); living longer/feeling better (n = 851, 81.5%); recommendation by cancer doctor (n = 797, 76.3%); closer monitoring (n = 528, 59.5%); fear of more side-effects (381,36.5%) or death (n = 337,32.3%); concerns about the treatment not working (n = 446,42.7%); increased hospital visits (n = 292, 28.0%); age (n = 355, 34.0%). Only 83 pts (9.3%) independently asked about participating in a CCT. Pts were asked about hypothetical participation in a CCT of a new drug that appeared safe but which could be better than/similar to/worse than standard treatment (ST). 687 (65%) pts reported they would consider participation but more than half 336 (51.3%) of those reconsidered when a subsequent question re-stated the possibility the study drug could be worse than ST. Of those previously offered a CCT most (n = 214, 68.8%) had decided without help. When making decisions about CCT participation; family (n = 175, 56.2%); internet (n = 67, 21.5%) and GP (n = 48, 15.4%) were frequent sources of support. Most sources encouraged (n = 169, 54.3%) or were neutral about participation (n = 72, 23.2%). Cancer doctors and specialist nurses scored highest in terms of pts’ trust about CCT information; 250 (69.8%) and 196 (59.4%) pts gave them full scores respectively.

**Conclusions:** Decisions about CCT’s are complex, based on personal and altruistic factors and may be influenced by the type and detail of information given and by who provides it. Few pts we surveyed asked about a CCT, but most who had been offered a CCT had participated.

**Legal entity responsible for the study:** Catherine M. Kelly

**Funding:** Cancer Trials Ireland with funding from Abbvie, Bayer, Amgen and Inveva

**Disclosure:** All authors have declared no conflicts of interest.

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**Table: 1471P Academic clinical research: Enough players to get out there?**

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<td><strong>C. Caprazzol, S. Campora, S. Pirondi, G. Gentili, A. Guarnera, C. Tavernini, M. Manuela</strong></td>
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<td><strong>1Gruppo Italiano Data Manager (GIDM), Modena, Italy, 2XCON plc, Milan, Italy,</strong></td>
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<td><strong>3Istituto Italiano di Ricerche per le Malattie Infettive, Modena, Italy, 4Cancer Institute of the University of Milan, Modena, Italy, 5ACU Careggi, Florence, Italy</strong></td>
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**Background:** The European Regulation 536/2014 definitively establishes the equality between pharma-sponsored and academic clinical research, raising the bar of standards for non-profit trials. Italy has always been known for the quality of its studies; our researchers have produced the 3.9% of world scientific papers in 2015-16 and 4% were among the 2016 world’s most influential scientific minds. However, the new compelling rules imposed by law make these great minds lacking in the absence of well-arranged staff, with dedicated professionals as clinical research coordinators (CRCs). Unfortunately, the national collective health contracts allow the employment of these experts only through atypical contracts that, due to new government requirements, will
soon be banned. We have decided to map how much the problem was widespread among Italian CRCs.

Methods: In November 2016 a web survey, focused on the imminent contracts’ expiration problem, has been sent to about 380 CRCs.

Results: Our survey was completed by 231 CRCs (77%). The majority of respondents (79%) work thanks to atypical contracts, while few can count on more stable ones (7.4% fixed term and 14.6% open-ended). Public hospitals have the more difficulties to ensure stable employment: only 25% of permanent contracts come from this type of structures and purely thanks to loopholes; indeed, despite their educational background, CRCs are employed almost exclusively as non-qualified administrative personnel. The 67.5% of respondents will be affected by the contract problem, with multiple expiration timing: 32% Jan-Apr 17; 23% May-Aug 17; 23% Sep-Dec 17; 17.3% from Jan 18. Interestingly, about 50 CRCs were unwilling to participate, demoralized from the age issue of the lack of professional recognition.

Conclusions: The need for clinical trials units officially and contractually recognized by competent authorities is a priority. The new government dispositions about atypical contracts could create a vacuum of skilled work force, which can hardly be covered by physicians. Since data are understated and the problem also affects another “big ghost” of clinical research (study nurse), in the absence of a permanent solution, Italy is unlikely to meet the required standards with a loss of appealing, but mostly with a slump of therapeutic options.

Legal entity responsible for the study: Gruppo Italiano Data Manager (GIDM)

Funding: None

Disclosure: All authors have declared no conflicts of interest.
SARCMA

14730
Encouraging activity of novel pan-KIT and PDGFRα inhibitor DCC-2618 in patients (pts) with Gastrointestinal Stromal Tumour (GIST)


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Background: Approved TKIs primarily inhibit either the KIT ATP binding pocket (exon 11/13/14) or a subset of activation loop mutations (exon 17/18) and do not demonstrate activity across both regions known to cause imatinib resistance in GIST. This leaves significant liabilities in inhibitory coverage of known KIT resistance mutations. DCC-2618 is a novel small molecule with a unique mechanism of action which targets the entire KIT receptor kinase switch network across a broad range of mutations which emerge on treatment with approved TKIs.

Methods: This is a dose-escalation study of oral DCC-2618 (QD or BID q28 days) followed by an expansion cohort in pre-treated TKI resistant GIST. During the escalation phase, FGFR2 scans were performed at baseline and after 3 wks of therapy; CT scans every 2 cycles. Next generation sequencing (NGS) of plasma cell-free (cf) DNA was performed throughout the study to quantify KIT, PDGFRα and other molecular alterations. Concordance of mutational status between plasma cfDNA and tumor tissue was assessed.

Results: 33/42 pts enrolled had KIT (30) or PDGFRα (3) driven GIST and received daily doses ranging from 40-400 mg. Mean prior lines of therapy was 4.8. The dose selected for expansion was 150 mg QD. Safety for all 42 pts was as follows: grade (G) 3/4 adverse effects (regardless of attribution, occurring in >1 pt) included anemia (15), asymptomatic lipase increase (>1.7x), hypertension (4), creatine phosphokinase (CPK) (2), lower GI hemorrhage (2). Two of the G3/4 lipase at 100 mg BID and 200 mg BID and one CPK at 150 mg QD were DLTs. Of 19 pts with KIT mutant GIST assessed by FGFR PET, 15 (79%) had a partial metabolic response per EORTC criteria. 2 out of 23 evaluable patients showed RECIST partial responses (PRs) and 6 out of 11 evaluable patients at 6 months had RECIST progression free survival of >6 months (pts on therapy at Cycle 10). NGS of plasma cfDNA revealed a reduction of mutation allele frequency (MAF) (in exons 9, 11, 13, 14, 17 and 18).

Conclusions: DCC-2618 showed encouraging disease control with objective responses and prolonged stable disease in heavily pre-treated GIST patients. The notable decrease in MAF of resistance mutations across all exons supports the use of DCC-2618 beyond imatinib resistance.

Clinical trial identification: NCT02571036

Legal entity responsible for the study: Dicaphera

Funding: Deciphera

Disclosure: All authors have declared no conflicts of interest.

14740
Improved overall and progression free survival after surgery in expert sites for sarcoma patients: A nationwide study of FSG/GETO/NETSARC

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Background: Sarcomas are rare but aggressive diseases. Specialized multidisciplinary management is not implemented for all patients in most countries. We investigated the impact of the surgery in a reference center on relapse and survival in the nationwide NETSARC/GETO/NETSARC study.

Methods: NETSARC (netsarc.org) is a network of 26 reference sarcoma centers with specialized MDTB, funded by the French National Cancer Institute to improve the outcome of sarcoma patients. Since 2010, presentation to an MDTB and second pathological review are mandatory for sarcoma patients. Patients’ characteristics and follow-up are collected in a database regularly monitored. Uni and multivariate analysis of prognostic factors for local relapse free survival (LRFS), relapse free survival (RFS) and overall survival (OS) were calculated.

Results: Of the 9,954 non-metastatic pts aged 0–15, with a first diagnosis of soft tissue and visceral sarcoma obtained between Jan 2010 and Dec 2014, 3505 (36%) and 6089 (63%) were operated within vs outside of one of the 26 NETSARC reference centers. The former group had worse prognostic characteristics (age, size, grade, depth < 0.0001 all). In univariate analysis, surgery within a reference center was associated with a better LRFS & RFS (median 60 vs 41 mos, and 25 vs 21 mos, respectively, logrank P < 0.001). LRFS and RFS were significant in all individual subgroups of quality of resection. (0, R1, R2, R unknown) (p < 0.001).

Surgery in reference center was an independent good prognostic factor for LRFS (HR: 0.67; 97.5% CI: 0.59–0.76; P < 0.001). LRFS was better for resection with margins ≤1 mm (HR: 0.79; 97.5% CI: 0.68–0.91; P = 0.01).

Conclusions: In this nationwide unselected population, the LRFS and RFS of sarcoma patients is worse than that reported in expert centers series. Surgery in reference center is associated with significant reduction of the risk of relapse and death.

Legal entity responsible for the study: NETSARC/French Sarcoma Group

Funding: INCA DIGOS

Disclosure: All authors have declared no conflicts of interest.

14750
A randomized clinical trial of adjuvant chemotherapy with doxorubicin, ifosfamide and cisplatin (API), followed by radiotherapy versus radiotherapy alone in patients with localized uterine sarcomas (SARCGYN study). Update at 10 years

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1Department of Cancer Medicine, Institut de Cancérologie Gustave Roussy, Villejuif, France, 2Department of Biostatistics, Institut de Cancérologie Gustave Roussy, Villejuif, France, 3Medical Oncology, Institut Bergonie, Bordeaux, France, 4Medical Oncology, Institut Universitaire du Cancer-Tourette-Carcassonne, Toulouse, France, 5Medical Oncology, Institut de Cancérologie de Lorraine - Alexis Vautrin, Vandoeuvre Les Nancy, France

Background: SARCGYN was a phase III study which compared adjuvant polychemotherapy followed by pelvic radiotherapy (RT) (arm A) versus RT alone (arm B). The study met its primary end point (3-year progression-free survival (PFS)) and showed a statistical increase of the 3-year PFS in the chemo+RT arm (A) vs radiation arm (B) (55% and 41% respectively, [P = 0.048]) after a median follow-up of 4.3 years (Ann Oncol 2013). Secondary end-point was overall survival (OS) that required a longer follow-up.

Methods: Patients with FIGO stage ≤III US, and physiological age ≤ 65 years were randomized after complete surgery and normal thoracic and abdominal pelvic CT scans between CT and no CT, with a stratification between carcinosarcomas (CS) versus others. Study was stopped earlier because of lack of recruitment. All patients received pelvic RT (45 grays), vaginal brachytherapy was optional. Chemotherapy consisted in four cycles of doxorubicin 50 mg/m², d1; ifosfamide 3 g/m²/day d1-2; cisplatin 75 mg/m², d3; G-CSF q 3 weeks.

Results: Eighty-nine patients were included: 39 in arm A and 42 in arm B; 52 stage I, 16 stage II, and 13 stage III; 53 leiomyosarcomas, 9 undifferentiated sarcomas, and 19 carcinosarcomas. API was toxic with two toxic deaths and one acute leukemia. After a median FU of 9.5 years (0.3-15.1), 42/81 patients relapsed, 16 in arm A, and 26 in arm B, and 38 died, 16 in arm A, and 22 in arm B. The 5-year OS is 74% in arm A and 60% in arm B, and the difference is not significant (p = 0.16).

Conclusions: In this trial interrupted at an early stage and with a longer follow-up, there is no statistical impact of API adjuvant CT on OS. The two toxic deaths and the integration of carcinosarcomas may have impacted on the global prognosis. A selection
of a specific uterine population and a less toxic chemotherapy for future studies are mandatory.

Clinical trial identification: NCT0162721

Legal entity responsible for the study: Institut de Cancérologie Gustave Roussy

Funding: Association pour la Recherche contre le Cancer; Chugai Pharma

Disclosure: P. Feuter: Advisory board: Roche and Pharmacarm. S. Piperno-Neumann: Travel grants: Pharmamar. N. Varoutsis: Traveling grants: Pharmamar. N. Varoutsis: F. Duffaud: Consultancy work: Lilly, Pharmacarm, Bayer, Novartis Travel grants: Pfizer, Pharmacarm. All other authors have declared no conflicts of interest.

1476PD Tumour necrosis and clinical outcomes following neoadjuvant therapy in soft tissue sarcoma (STS)

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Background: Tumour necrosis following chemotherapy is prognostic in bone sarcoma, but remains undefined in STS.

Methods: We searched MEDLINE, MEDLINE in progress, EMBASE and Cochrane to identify studies that investigated neoadjuvant therapy in STS. Eligible studies were required to have data on survival outcomes based on tumour necrosis in the restaged specimen, or provided individual patient data. Hazard ratios (HR) for relapse free (RFS) and overall survival (OS) were calculated with stratified analysis for recurrence at 3 years and for death at 5 years were pooled in a random effect meta-analysis. Association between patient characteristics and attainment of ≥ 90% necrosis were explored with logistic regression.

Results: 21 studies comprising 1,644 patients were included in this analysis. Location of the tumor included the extremities in the majority (n = 1,459; 89%). Induction regimens included chemotherapy/radiation (n = 813; 49%), chemotherapy alone (n = 418; 25%), chemotherapy/caffeine (n = 81; 5%), radiotherapy alone (n = 78; 4%), isolated limb perfusion (ILP) with (n = 28; 2%) or without radiation (n = 208; 13%), and targeted therapy/radiotherapy (n = 18; 1%). Utilizing a cut-off of 90% necrosis, patients with ≥ 90% tumour necrosis had significantly reduced risk of recurrence at 3 years (OR (95% CI): 0.20-0.44; p < 0.0001) and had improved 5-year OS (OR (95% CI): 0.23; 0.63; p < 0.0001). Limiting the analysis to studies with reported HR (n = 6), patients with ≥ 90% necrosis also had a lower risk of recurrence (HR 0.68; 95% CI: 0.49-0.94; p = 0.02) and death (HR 0.54; 95% CI: 0.41-0.71; p < 0.0001). There was no significant association between age, gender, and histologic subtype with attainment of ≥ 90% necrosis. Compared to other neoadjuvant modalities, ILP was associated with higher odds of achieving ≥ 90% necrosis (OR (12.1; 95% CI: 3.69-39.88; p < 0.0001).

Conclusions: Tumour necrosis ≥ 90% following neoadjuvant therapy is associated with reduced recurrence risk and improved overall survival in patients with STS.

Legal entity responsible for the study: Princess Margaret Cancer Centre

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1477PD Prognosis of desmoid tumours initially managed with surveillance only at all anatomical locations


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Background: Desmoid tumours are locally aggressive mesenchymal tumours that lack metastatic potential. Tumour behaviour is unpredictable and varies along a spectrum depending on the location and stage of the disease.

Methods: Retrospective multicenter study of 12,262 patients and treated between 1980 and 2015 in one of 22 French Referral Sarcoma Center and enrolled in the “Conticabase”. Diagnoses were systematically reviewed by expert pathologists and entities classified according to the 2015 WHO Classification.

Results: The median follow-up was 4.9 years (95% CI: 4.7-5.0). TUMS included 13 entities: synovial (S760 cases; 7.4%/5-y OS: 64%), myxoid LPS (46.2%/5-y OS:88%), PNET (203; 2.0%/5-y OS: 58%), round cell LPS (183; 1.8%/5-y OS: 70%), alveolar RMS (122; 1.2%/5-y OS: 25%), malignant retinoblastoma (86; 0.8%/5-y OS: 77%), clear cell sarcoma (63; 0.9%/5-y OS: 67%), LGFMS (60; 0.6%/5-y OS: 82%), desmoplastic round cell tumor (56.5%/5-y OS: 11%), EMSCS (54; 0.5%/5-y OS:78%), ASPS (48; 0.5%/5-y OS: 66%), and sclerosing epithelioid fibrosarcoma (28; 0.3%/5-y OS: 70%). All TUMS (2,143 cases; 20.8%) are associated with younger age (40.6 versus 60.0; p < 0.0001), low rate of predisposing conditions (0.01% vs 22.3%, p < 0.0001), and higher rate of N involvement (4.7% vs 1.3%, p < 0.0001 and higher rate of lymph node metastasis (11.9 vs 6.7%, p < 0.0001). Survival was significantly lower in patients with neurofibromatosis I disease (11.9 vs 6.7%, p < 0.0001). N1 disease was associated with lower rate of local relapse (18.1% vs 26.0%; p < 0.0001) but a higher rate of metastasis relapse (42.0 vs 30.7%; p < 0.0001).

Conclusions: TUMS display specific pattern compared to other sarcomas. Second opinion by expert pathologist and use of molecular biology confirmatory test are of major importance to recognize this population and discuss multimodal approach at early stage of the disease.

Legal entity responsible for the study: Centre Oscar Lambret, Lille, France

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1479PD Phase II study of TAS-116, an oral inhibitor of heat shock protein 90 (HSP90), in metastatic or unresectable gastrointestinal stromal tumor refractory to imatinib, sunitinib and regorafenib

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Background: Mutated KIT and PDGFRA in gastrointestinal stromal tumor (GIST) rely on HSP90 for their functional stability; therefore, HSP90 is a rational therapeutic target in treating GIST in patients (pts) acquired resistance to approved tyrosine kinase

chest wall or upper extremity caused significantly more pain than other locations (p = 0.01), while pregnancy-associated desmoid tumours caused significantly less pain (p = 0.04).

Conclusions: Patients with desmoid tumours can be managed with surveillance only, but a large minority still needs treatment after an initial period of surveillance. Pain and tumour growth are the most common indications to start treatment after initial surveillance.

Legal entity responsible for the study: Winnette van der Graaf

Funding: None

Disclosure: All authors have declared no conflicts of interest.
A phase 2 study of CBM305 and atezolizumab in NY-ESO-1+ soft tissue sarcoma: Interim analysis of immunogenicity, tumor control and survival

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Background: CBM305 is an active immunotherapy designed to generate and expand anti-NY-ESO-1+ immunologic response (IR). CBM305 consists of a dendritic cell-targeting leukocytic antigen vector encoding NY-ESO-1 (LV305), and a boost with an NY-ESO-1+ combinator protein plus GLA-SE (G305), a TLR-4 agonist. Phase 1 studies of LV305 and CBM305 showed this approach is safe, generates IR and appears to impact survival with 81% 1-yr survival in NY-ESO-1+ sarcoma patients (pts) following LV305 treatment. We evaluated efficacy and IR for combination of CBM305 (C) and atezolizumab (A) or A alone in NY-ESO-1+ synovial sarcoma (SS) and myxoid round cell liposarcoma (MRCL).

Methods: A prospective randomized open label phase 2 study of C (LV305 Intradermal Days 0, 14, 42, 70 + G305 Intramuscular Days 28, 58, 64 then qwk up to one year) + A (120mg IV qwk vs. A alone in locally advanced or metastatic NY-ESO-1+ SS/ MRCL. Primary endpoints are progression free survival (PFS) and overall survival (OS) with secondary endpoints of safety, IR, and response rate.

Results: As of December 30, 2016, 58 patients were enrolled. A prespecified interim analysis of PFS included the first 36 pts with median 7.0 mos follow up (Arm A+C: mean age 47 yrs, 78% SS, 100% metastatic, 78% = = 2 chemotherapy; Arm A: mean age 44 yrs, 56% SS, 67% metastatic, 56% = = 2 chemotherapy). Combination A+C was well tolerated. Clinical benefit was similar between arms (Arm A+C: 8/18 pts with SD, 1 pt PR). Pts received a median of 9 cycles (Arm A+C: 7/18 pts). In addition, anti-NY-ESO-1 IR seen in 10/19 (53%) pts Arm A+C vs 3/12 (25%) pts Arm A by T Cell ELISPOT, and 92/42 (41%) pts Arm A+C vs 0% Arm A by antibody ELISA. Pts with IR had target lesion response of 2% compared to 18% in pts without IR based on preliminary ANOVA model based analysis. No deaths observed in pts with induced anti-NY-ESO-1 IR (vs SD 28.7 IR pts vs 25.7 IR pts).

Conclusions: In the interim analysis, Arm A+C resulted in a higher level of anti-NY-ESO-1 IR’s when compared to Arm A, pts with IR tend to have better target lesion control. Early data indicate that induction of anti-NY-ESO-1 IR 1 may be associated with better survival.


Legal entity responsible for the study: Immune Design

Funding: Immune Design

disease at 4 months indicating that palbociclib had not reached the primary endpoint to justify continuing accrual after the 1st step of the study.

Conclusions: Palbociclib has no significant activity as a single agent in advanced GIST with p16/Cdk4/6 loss. Prognostic value of Cdk4/6 loss in the whole population will be presented at the meeting.

Clinical trial identification: NCT01907607

Legal entity responsible for the study: Institut Bergonié

Funding: INCA

Disclosure: All authors have declared no conflicts of interest.

Notch pathway inhibition with LY3039478 in soft tissue sarcoma (STS) and gastrointestinal stromal tumours (GIST)


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Background: LY3039478 (LY) is an orally bioavailable selective Notch inhibitor (Notch-1,-4). Here we report on safety, pharmacodynamics (PD), and anti-tumour activity of LY in patients (pts) with STS/GIST.

Methods: This ongoing, multi-part, phase 1 trial enrolled pts with refractory advanced or metastatic STS and GIST, measurable disease, ECOG score ≤1, and baseline tumour tissue. Eligible pts received LY 50 mg three times per week (TIW), for a 28-day cycle until disease progression. Safety assessments were based on CTCAE V4.0. Tumour responses were assessed using RECIST 1.1 and Choi criteria. Primary objectives are to confirm the recommended phase 2 dose of LY and document antitumour activity. Secondary objectives are safety and toxicity, PD, progression-free survival (PFS) and overall survival (OS).

Results: 63 pts have been enrolled and received LY (24 males, 39 females; median age 58, range 31-76). 26 pts had leiomyosarcoma (LMS), 9 liposarcoma, 7 pleomorphic sarcoma, 6 angiosarcoma, 5 rhabdomyosarcoma and 10 GIST. 18 out of 39 (46%) pts with evaluable tumour samples were positive for Notch 1, 5% and 13% were positive for Notch 2, NICD, and Notch 3, respectively. PER RECIST, 2 out of 53 pts with STS had unconfirmed PR, and 20 SD. In GIST group, 4 pts had SD. Using Choi Criteria, 5 pts in STS had unconfirmed PR. Overall median PFS was 1.74 months (95% CI: 1.68-2.60) and consistent across histology groups (median PFS=22-23, 1.91 and 1.68 months for LMS, GIST and other STS, respectively). PFS rate at 3 months was 42% in LMS, 26% in GIST and 15% in other STS, respectively. OS and biomarker/histologic analyses for LMS, GIST and other STS, respectively). PFS rate at 3 months was 42% in LMS, 26% in GIST and 15% in other STS, respectively. OS and biomarker/histologic analyses for LMS, GIST and other STS, respectively). PFS rate at 3 months was 42% in LMS, 26% in GIST and 15% in other STS, respectively. OS and biomarker/histologic analyses for LMS, GIST and other STS, respectively). PFS rate at 3 months was 42% in LMS, 26% in GIST and 15% in other STS, respectively. OS and biomarker/histologic analyses for LMS, GIST and other STS, respectively).

Conclusions: LY suggested activity in pts with STS and GIST and has a manageable safety profile.


Legal entity responsible for the study: El Lilly and Company

Funding: El Lilly and Company


A matching-adjusted indirect comparison of trabectedin and pazopanib for the treatment of advanced, metastatic leiomyosarcoma


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Background: Trabectedin (T) and pazopanib (P) are approved treatments for locally advanced or metastatic leiomyosarcoma (L-mSTS). In the absence of head-to-head randomized controlled trials (RCTs); a matched indirect comparison (MIC) was performed to assess potential differences in clinical efficacy between the treatment groups.

Methods: MIC was performed by extracting baseline characteristics from two phase III RCTs: SAR 3007 (T) and PALETTE (P): individual patient level data (IPD) was available for T only aggregated was published for P. Excluding those T patients who did not meet inclusion criteria for PALETTE, a sample size of 372 L-mSTS patients (T = 263, P = 109) was generated. Of all baseline characteristics, only time since diagnosis (≥30 vs. <30 months), age (≥65 vs. <65 years), and body weight (≥77 vs. <77 kilograms), were statistically significant outcome predictors with T. The generalized method of moments (GMM) was used to optimally match cohorts for evaluation of
differences in overall survival (OS), progression-free survival (PFS), and safety. Statistical analysis was performed using “R”.

Results: There was no statistically significant difference in PFS [HR = 0.82, (95% CI 0.63-1.06), p = 0.131], or OS [HR = 0.86, (95% CI 0.64-1.18), p = 0.361]. The percentage of patients with post-progression therapies was higher in T (74.9%) vs. P (99%) group. In the subgroup with PFS ≥ 2 months, patients treated with T experienced significantly improved median PFS (11.2 months vs PFS 8.4 months, HR = 0.477 [95% CI: 0.3007 – 0.7434], p < 0.001 and were significantly more likely to achieve long term survival (OS ≥ 18 months): 45.8% vs. 33.7% (95% CI: 23.5%-48.3%), p < 0.025. Increased melysosuppression and hepatotoxicity observed with T whereas diarrhea, hypertension, pulmonary toxicity/pneumothorax, and neurotoxicity were observed with P.

Conclusions: The MACM model warrants further investigation and validation. No differences in mPFS or mOS were noted in a MACM comparison. Among patients achieving long term disease control (PFS > 6 mo), T significantly increased mPFS and the proportion of patients achieving prolonged overall survival (OS > 18 mo). Differences in the safety profile were highlighted by this indirect comparison.

Legal entity responsible for the study: Janssen Sciences Affairs, LLC, Pharma Mar S.A., LLC.

Funding: Janssen Sciences Affairs, LLC, Pharma Mar S.A., LLC.


Natural history of alveolar soft part sarcoma (ASPS): Impact of brain metastases and role of anti-angiogenic therapies (AAT)

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Background: ASPS is a rare sarcoma subtype with clinical specificities, such as an indolent behavior, brain metastasis and resistance to doxorubicin. AAT have shown clinical activity in this setting, but is little known the optimal therapeutic strategy, and the management of brain metastasis (BM).

Methods: We retrospectively analyzed patients (pts) treated in 3 referral centers of the French Sarcoma Group. Factors associated with BM development and overall survival (OS) were analyzed. In addition, progression-free survival (PFS) under AAT in pa-

Results: We identified 75 pts (median age at diagnosis: 23 (5.96 years, 61% females). Among those, 31 (41%) pts had documented synchronous lung metastasis (LM), and none had BM. Median OS in pts with localized and metastatic disease were 279 months, (95% CI: 279-740) and 74 months (95% CI: 62, 144) (Log-rank, p = 0.002, respectively. Only surgical complete resection (R0) was associated with better OS in pts with localized disease (HR = 4.3; (95% CI: 1.9, 9.3), p = 0.056). Fifty-two (69%) pts had documented LM in the course of the disease; among those, 13 (17%) pts developed BM within a me-

Conclusions: These data highlight the indolent course of the disease leading to BM, which turned a shift in the course of the disease, along with limited efficacy of AAT in this setting. Furthermore, they suggest that the appropriate timing for AAT intro-

Legal entity responsible for the study: Institut Gustave Roussy

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Disclosure: G. Malouf: Consulting: Pfizer, BMS, Novartis Research grant: Pfizer, Novartis. O. Mie: Speaker: Lilly; Roche Consulting: Amgen, Astra-Zeneca, Bayer, Blueprint, BMS, Lilly, Novartis, Pfizer, Roche, Servier. J-P. Spano: conflict of interest with the following companies: Pfizer, BMS, MSD, Roche. J-Y. Blay: Research support: Novartis, Roche, GSK, Bayer, Pfizer. A. Lecesne: Honoraria: Amgen, Novartis, Pharmamuc, Pfizer, Lilly. All other authors have declared no conflicts of interest.

Treatment patterns, clinical outcomes and prognostic factors of visceral angiosarcoma (V-AS): A report from the Asian Sarcoma Consortium (ASC)


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Background: We previously reported on the real world treatment and outcomes of 423 angiosarcoma pts in Asia. In this current report, we focus on the 173 pts with V-AS and evaluate the treatment patterns and prognostic factors associated with this disease subset.

Methods: This is a retrospective chart review of V-AS pts seen at 8 Asian academic study sites. Survival analysis is measured from date of presentation to the study site.

Results: Median study follow-up was 8.7 mths. Median age 52 yrs; 86% of pts presented with primary disease to study site. 42% (n = 75) had localized disease and 56% (n = 97) had locally advanced/unresectable or metastatic disease; disease status was unknown for 3 pts. Distribution of primary site as follows, liver (n = 38, 22%), cardiovascular sys-

Conclusions: This study highlights the heterogeneity and treatment challenges of vis-

Legal entity responsible for the study: National Cancer Centre Singapore

Funding: None

Disclosure: R. Quek: Grants/research support: Novartis, Pfizer, Janssen, Bayer and Eisai. Honoraria/consultation fees: Novartis, Bayer, BMS, Merck, Roche and Eisai. Participation in a company sponsored speaker’s bureau: Novartis, Bayer, Merck and Eisai. All other authors have declared no conflicts of interest.
Background: Primary cardiac sarcoma (PCS) is a rare but often fatal disease. The current study aimed to analyze the impact of baseline demographics, local and systemic therapies in a contemporary cohort.

Methods: Clinical records of PCS across five institutions in three continents were retrospectively reviewed and collected. Kaplan-Meier was used to estimate survival. Cox proportional hazard model was used to associate variables to progression-free survival (PFS) or overall survival (OS).

Results: 47 pts with PCS (1996-2016) with a median follow-up of 12.9 months were identified. The median age at diagnosis was 41 (range 18-79); 43% (n=20) presented with metastatic disease. Tumor equally originated from right- (n = 23) and left-sided heart (n = 23). The common histologies were angiosarcoma (n = 18, 38%), intimal sarcoma (n = 8, 17%), and sarcoma NOS (n = 10, 21%). 66% (n = 31) had surgical (S) treatment for PCS, and only 4 (13%) pts had 80 resection. The median primary lesion size was 49 mm (26-84 mm). 70% (n = 33) of pts received at least one line of chemotherapy (C), and 51% (n = 24) received multi-modality treatment (43% S+C, 4% S+C + XRT, 2% S+C + XRT). The median OS was 17.7 ms (95% CI 12.4-21.8 ms). For all pts, age <7.43, p = 0.0002. In both datasets, 5-year overall survival (OS) did not significantly differ between the two data-sets (R:38/223, 78.5% vs. W: 32/218, 80.9%, p = 0.561), but did significantly differ between the subtypes (R: P = 0.005, W: p = 0.001). In both datasets, 5-year overall survival was poorest in PLPS (R: 8/20, 50.3% and W: 16/34, 44.5%), but in the Rotterdam cohort MLPS (16/77, 83.3%), MLPS (12/95, 84.9%) and WDLPs (3/79, 41%, p = 0.081). Distant metastases (DM) were most commonly observed in PLPS in both datasets (5-year DM /survival R: 2/90, 50.3% and W: 16/34, 44.5%), but in the Rotterdam cohort MLPS (16/77, 83.3%) was the second most common subtype with DM, compared to WDLPs (2/10, 62.5%) in Warsaw. DM in WDLPs was rare in both datasets (R:3/113, 96.3%, W: 1/79, 98.5%). 5-year overall survival (OS) did not significantly differ between the two datasets (R: 38/223, 78.5% vs. W: 32/218, 80.9%, p = 0.561), but did significantly differ between the subtypes (R: P = 0.005, W: p = 0.001). In both datasets, 5-year overall survival was poorest in PLPS (R:8/20, 57.9%, W: 15/34, 45.7%) and WDLPs (R:4/13, 98%, W: 3/10, 44.4%), but followed by WDLPs (R:16/77, 75.6%, W: 13/95, 83.1%) and WDLPs (R: 10/113, 88.2%, W: 1/79, 98.5%).

Conclusions: The prognosis of PCS remains poor without significant improvement in OS compared to historical levels. Further research is required for this rare entity.

Legal entity responsible for the study: Hee Kyung Ahn

Disclosure: All authors have declared no conflicts of interest.

Table: 1490P Prognostic factors for all pts

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 65</td>
<td>7.43 (2.54-21.72)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Metastatic disease at diagnosis</td>
<td>1.87 (0.90-3.88)</td>
<td>0.09</td>
</tr>
<tr>
<td>Multi-modality treatment</td>
<td>0.64 (0.32-1.27)</td>
<td>0.20</td>
</tr>
<tr>
<td>Angiosarcoma histology</td>
<td>1.58 (0.72-3.47)</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Conclusions: The prognosis of PCS remains poor without significant improvement in OS compared to historical levels. Further research is required for this rare entity.

Legal entity responsible for the study: Not applicable

Disclosure: Funding: None

The sarcoma policy checklist: Focusing policy efforts on sarcoma

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10The Health Policy Partnership, London, UK; 11SPLA, Wollongong, Germany

Background: The Sarcoma Policy Checklist was developed by a multi-stakeholder group of experts to help policymakers prioritise actions to close the gap in access to high-quality information and care for sarcoma patients in Europe.

Legal entity responsible for the study: The Health Policy Partnership

Disclosure: Funding: None

Conclusions: Surgical resection and multidisciplinary treatment were associated with better survival in patients with primary cardiac sarcomas. Aggressive multidisciplinary approaches may have a role in subset of patients with primary cardiac sarcomas.

Annals of Oncology
Methods: Experts defined five key areas where policy efforts are most needed to improve the care of sarcoma patients across Europe. A pragmatic review of the published literature was then conducted to determine to what extent recommendations were implemented in practice. Research focused on six countries (France, Germany, Italy, Spain, Sweden and the United Kingdom) and was complemented by local expert interviews.

Results: Five key priority areas were identified by experts: Each country should have designated, accredited centres of reference for sarcoma; specialised professional training should be provided to all health care professionals involved in sarcoma care; a multidisciplinary approach to care should be offered to every patient; greater incentives for research and innovation, and more rapid access to effective treatments are needed. Most countries have specialist sarcoma centres, however, there is often a lack of defined criteria to designate specialist centres and evaluate the quality of care. Professional training is a gap in all countries, as training on rare cancers is most often not included in the general medical curriculum or in oncologists’ training. More basic research is needed to understand the underlying epidemiology of sarcomas, and help focus research on effective treatments. Greater alignment between regulatory frameworks and access frameworks such as Health Technology Assessment is needed, particularly in terms of evidentiary requirements for new treatments.

Conclusions: The heterogeneity of sarcomas poses particular challenges to research, professional training and patient access to quality treatment and care. The creation of the European Reference Network (ERN) on sarcoma, and recent advances in defining essential requirements and patient-driven principles for sarcoma care will help improve the situation of sarcoma patients across Europe. This policy paper hopes to contribute to those efforts and help drive meaningful policy change to improve patient care.

Legal entity responsible for the study: The Health Policy Partnership Ltd

Funding: Eli Lilly and Company

Disclosure: N. Drove: Employment with Eli Lilly and Company, the pharmaceutical company that is funding this project. S. Bolden: Consultancy fees from Eli Lilly and Company as an employee of the Health Policy Partnership, which has led the coordination and policy writing for this project. S. Wait: Consultancy fees from Eli Lilly and Company as managing director of the Health Policy Partnership, which has led the coordination and policy writing for this project. All other authors have declared no conflicts of interest.

1494P Dermatofibrosarcoma protuberosans might not benefit from postoperative radiotherapy after local resection with negative margin

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Background: To evaluate the role of postoperative radiotherapy (RT) in the treatment of dermatofibrosarcoma protuberosans (DFSP) after local resection with negative margin.

Methods: We retrospectively analyzed 84 consecutively treated DFSP patients who received local resection (≤2cm) with negative margin from 2006 to 2016 in our institution. Statistical analysis was performed with a commercially available statistical software package.

Results: The median follow-up was 60 months (range, 10-201). For patients (28/84) with positive postoperative RT, four (4/28) patients were found to have local relapse, while three of them had ≤1 cm surgical margin. For patients without postoperative RT, four (4/56) patients had local failure. Postoperative RT failed to improve the local recurrence-free survival (LRSF) of DFSP after local resection with negative margin (Fisher-=0.431). Patients with fibrosarcomatous DFSP (FS-DFSP) were found to have lower local recurrence rate than DFSP (66.7% vs. 7.4%; Fisher=-0.023). Twenty-six patients were examined for ki-67, and positive range is 1-30%. Patients with high ki-67 expression (>15%) were found to have higher local recurrence rate than the others (80.0% vs 0%; Fisher=-0.001).

Conclusions: Postoperative RT did not improve the LRSF of DFSP after local resection with negative margin. FS-DFSP was more likely to have a local relapse than the other types. Ki-67 might become a good predictor for local control of DFSP.

Legal entity responsible for the study: Kai Xin Kaixin Du

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1495P Low-dose chemotherapy with methotrexate and vinblastine for desmoid tumors: A single institution experience

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Background: Desmoid tumor (DT) is a rare and locally invasive proliferative disease. Although, the absence of metastatic potential, it has the propensity for locally invasive growth and recur. Chemotherapy may be considered in inoperable and/or recurrent disease.

Methods: Patients with histological diagnosis of DT and treated with weekly low-dose chemotherapy with vinblastine and methotrexate between January 1998 and December 2015 were identified and their medical records were analyzed.

Results: Of 23 patients analyzed, most of them were women (female-to-male ratio 2.8:1). The median age at presentation was 29 years (range, 18-59 years). Tumors location was: thoracoabdominal wall (n: 11, 47.8%), extremities (n: 7, 30.4%), abdominal cavity (n: 1, 4.3%), and head and neck (n: 4, 17.3%). Tumor sizes were documented in 18 cases and ranged from 3 to 50 cm in largest linear dimension (median, 14 cm). Eight (34.7%) female had pregnancy history and 2 (8%) had familial adenomatous polyposis history. Eleven (47.8%) underwent surgery as first-line treatment. Five (21.7%) patients received first-line treatment with vinblastine and methotrexate, four (17.3%) patients as second-line, and 14 (60.8%) patients as third and fourth-line. Fourteen (60.8%) patients had stable disease, four (17.3%) had partial response, and five (21.7%) patients had progressive disease during chemotherapy treatment. After a median follow-up of 25 months, 12 patients had progression disease and 2 patients died. The median PFS was 29 months, without any progression after 32 months. Conclusions: Discussion: Weekly low-dose chemotherapy with vinblastine and methotrexate appears to have significant activity. Chemotherapy could be an acceptable alternative to radical surgery in selected patients with desmoid tumors.

Legal entity responsible for the study: INCA

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Background: Treatment of soft tissue sarcoma (STS) with long-term systemic therapy can be limited by cumulative toxicity. Treatment T for prolonged courses without the cumulative toxicity has been previously described from clinical trials. Here we report the efficacy and safety for patients (pts) treated long term (>6 months) in a real-world setting in the T Expanded Access Program from 2005-2010.

Methods: In this retrospective analysis of pts with pre-treated, relapsed/refractory STS of multiple histologies treated >6 mo with T (1.5 mg/m² iv q4wks), we compared pts treated 6-12 mo and >12 mo.

Results: Of 1803 pts, 401 (21.6%) remained on treatment >6 mos; 268 (14.5%) for 6-12 mo and 133 (7.2%) >12 mo. Demographics did not differ. Leiomyosarcoma or liposarcoma were the most common histologies. The mOS (mos) was 18.1 and 47.0, ORR was 7.8% and 6.8%, and clinical benefit rate (CBR=CR+PR+SD) (95%CI) was 47.4 (41.5-53.6) and 43.8% (30.1-47.2) in the 6-12 mo and >12 mo groups, respectively. The incidence of adverse events (AEs) and serious adverse events (SAEs) were similar in both groups (Table). The most common grade 3/4 AEs occurring in ≥5% were neuropenia, thrombocytopenia, anemia, ALT/AST increase, fatigue and nausea. A majority received dose reduction or delay; the primary reason for treatment discontinuation was disease progression. The longest observed duration of treatment was 55 mo (84 cycles), synovial sarcoma and 54 mo (73 cycles), uterine leiomyosarcoma.

Table: 1497P Safety and Efficacy

<table>
<thead>
<tr>
<th></th>
<th>6-12 Months</th>
<th>&gt;12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Treatment Duration (mo), range</td>
<td>8.4 (6.2)</td>
<td>16.3 (12.5)</td>
</tr>
<tr>
<td>Treatment Response, Complete response, n (%)</td>
<td>1 (0.4)</td>
<td>3 (2.3)</td>
</tr>
<tr>
<td>Partial response, n (%)</td>
<td>20 (7.5)</td>
<td>6 (4.5)</td>
</tr>
<tr>
<td>Stable disease, n (%)</td>
<td>106 (39.6)</td>
<td>42 (31.6)</td>
</tr>
<tr>
<td>Progressive disease, n (%)</td>
<td>20 (7.5)</td>
<td>12 (9.0)</td>
</tr>
<tr>
<td>Not available, n (%)</td>
<td>121 (45.1)</td>
<td>57 (20.6)</td>
</tr>
<tr>
<td>Treatment-emergent adverse events (TEAEs)</td>
<td>225 (84.0)</td>
<td>119 (89.5)</td>
</tr>
<tr>
<td>Serious TEAEs</td>
<td>88 (32.9)</td>
<td>47 (35.3)</td>
</tr>
<tr>
<td>Treatment discontinued</td>
<td>255 (95.1)</td>
<td>103 (77.4)</td>
</tr>
<tr>
<td>Due to disease progression</td>
<td>192 (71.6)</td>
<td>72 (54.1)</td>
</tr>
<tr>
<td>Due to adverse event</td>
<td>10 (3.7)</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>Patients with cycle delay</td>
<td>154 (57.5)</td>
<td>82 (61.7)</td>
</tr>
<tr>
<td>Patients with dose reduction</td>
<td>172 (64.2)</td>
<td>104 (78.2)</td>
</tr>
</tbody>
</table>

Conclusions: T can be safely administered and well tolerated in pts who receive a prolonged duration (>6 mo) of therapy. Improved mOS may be achieved in pts who experience prolonged disease stabilization following T but adjustments in dose or schedule is frequently required.

Clinical trial identification: NCT00210665

Legal entity responsible for the study: Janssen Research & Development, LLC

Funding: Janssen Research & Development, LLC


1497P Efficacy and safety of trabectedin in an elderly patient subgroup (≥65 years) with advanced leiomyosarcoma (LMS) or liposarcoma (LPS) from the Expanded Access Program (EAP)


Background: Elderly patients (pts) (≥65 yrs) with soft tissue sarcoma may have limited treatment options due to increased comorbidities and toxicities from available therapeutic agents. Previous retrospective analyses have suggested that trabectedin (T) has similar safety and efficacy outcomes irrespective of pt age.

Methods: In this multicenter, open-label study, pts received IV T (1.5 mg/m²) every 3 wks. We retrospectively analyzed the efficacy and safety of T in pts ≥65 yrs treated from 2005-2010 on this EAP.

Results: Mean age was 71.0 and 49.0 in the ≥65 vs <65 yrs group, respectively. The OS, ORR, and CBR of 78 (43.1%) and 313 (40.1%) in the ≥65 group. The longest observed duration of treatment was 55 mo (84 cycles), synovial sarcoma and 54 mo (73 cycles), uterine leiomyosarcoma. We retrospectively analyzed the efficacy and safety of T in pts ≥65 yrs treated from 2005-2010 on this EAP.

Results: Mean age was 71.0 and 49.0 in the ≥65 vs <65 yrs group, respectively. The OS, ORR, and CBR of 78 (43.1%) and 313 (40.1%) in the ≥65 group. The longest observed duration of treatment was 55 mo (84 cycles), synovial sarcoma and 54 mo (73 cycles), uterine leiomyosarcoma. We retrospectively analyzed the efficacy and safety of T in pts ≥65 yrs treated from 2005-2010 on this EAP.

Conclusions: The efficacy and safety profile of T in pts ≥65 yrs was similar to that observed in pts <65 yrs in this EAP. Based upon this real world experience, T should be considered as a treatment option for elderly pts with soft tissue sarcoma and good performance status irrespective of age.

Clinical trial identification: NCT00210665

Legal entity responsible for the study: Janssen Research & Development, LLC

Funding: Janssen Research & Development, LLC


1498P The routine real-life use of trabectedin (T) in patients with advanced soft tissue sarcoma (STS) across Europe: An analysis of overall vs. per country results from Y-IMAGE study

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Background: The prospective, non-interventional, phase IV Y-IMAGE study evaluated the use of T in real-life clinical practice across Europe in patients with advanced STS.

Methods: Data from adult STS patients treated with T 1.5 mg/m² given as 24-h iv infusion were collected. Patients must have received at least 1 cycle of T and currently be on T treatment. The primary endpoint was progression-free survival (PFS) as defined by investigators. The analyses were conducted in the overall population (OP) and in data from adult STS patients treated with T 1.5 mg/m² given as 24-h iv infusion were collected. Patients must have received at least 1 cycle of T and currently be on T treatment. The primary endpoint was progression-free survival (PFS) as defined by investigators. The analyses were conducted in the overall population (OP) and in.
and separately in countries with the highest recruiting rate to cover inter-country vari-
ations: France (F), Germany (G), Italy (I) and the UK.

Results: A total of 218 patients from 41 centers and 9 European countries were eval-
uated. Demographics and baseline characteristics of patients recruited in the 4 coun-
tries of interest were well-balanced and comparable to those observed in OP. Patients
received a median of 6 cycles of T (range: 1-44), mostly on an outpatient basis (n
¼ 23; Germany, n
¼ 26. NR, not reached.

Table: 1499P

<table>
<thead>
<tr>
<th>Full analysis set, n (%)</th>
<th>France (n = 26)</th>
<th>Germany (n = 29)</th>
<th>Italy (n = 69)</th>
<th>UK (n = 26)</th>
<th>Overall population (n = 218)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at study entry (years); Median (range)</td>
<td>58.5 (22-77)</td>
<td>58 (23-79)</td>
<td>59 (26-79)</td>
<td>56.6 (25-73)</td>
<td>58.0 (21.0-79.0)</td>
</tr>
<tr>
<td>Female</td>
<td>15 (57.7)</td>
<td>15 (51.7)</td>
<td>44 (63.8)</td>
<td>13 (50.0)</td>
<td>123 (56.4)</td>
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<td>Histology (≥10% of patients)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Leiomyosarcoma</td>
<td>11 (42.3)</td>
<td>11 (37.9)</td>
<td>29 (42.0)</td>
<td>16 (61.5)</td>
<td>92 (42.2%)</td>
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<tr>
<td>Liposarcoma</td>
<td>5 (19.2)</td>
<td>–</td>
<td>23 (33.3)</td>
<td>7 (26.9)</td>
<td>51 (23.4)</td>
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<tr>
<td>Synovial sarcoma</td>
<td>4 (15.4)</td>
<td>5 (17.2)</td>
<td>–</td>
<td>–</td>
<td>23 (10.6%)</td>
</tr>
<tr>
<td>Cycles per patient Median (range)</td>
<td>5.5 (2-29)</td>
<td>6.0 (2-18)</td>
<td>6.0 (1-30)</td>
<td>10.5 (1-44)</td>
<td>6.0 (1-44)</td>
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<tr>
<td>Cumulative dose received mg/patient</td>
<td>12.1 (7.3-48.2)</td>
<td>20.8 (5.6-51.0)</td>
<td>14.3 (1.9-60)</td>
<td>26.2 (3-116.4)</td>
<td>14.7 (1.8-116.4)</td>
</tr>
<tr>
<td>Cycle duration (days)</td>
<td>24.9 (21-41)</td>
<td>26.8 (21-44.4)</td>
<td>23.7 (20.5-32.4)</td>
<td>24.2 (21-30.6)</td>
<td>24.1 (20-47.5)</td>
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<tr>
<td>Dose intensity (mg/m²/week)</td>
<td>0.7 (0.2-1.0)</td>
<td>0.6 (0.4-1.1)</td>
<td>0.6 (0.3-1.0)</td>
<td>0.7 (0.5-1.0)</td>
<td>0.7 (0.2-1.1)</td>
</tr>
<tr>
<td>Median PFS (months) [95% Confidence interval]</td>
<td>7.6 [3.3-11.2]</td>
<td>5.9 [3.4-10.2]</td>
<td>6.8 [3.4-10.2]</td>
<td>8.3 [5.5-11.4]</td>
<td>5.9 [4.9-7.8]</td>
</tr>
<tr>
<td>Objective response rate (ORR) (Complete + partial response) [95% Confidence interval]</td>
<td>6 (23.1) [9.0-43.6]</td>
<td>9 (31.0) [15.3-50.8]</td>
<td>15 (21.7) [12.7-33.3]</td>
<td>10 (38.5) [20.2-59.4]</td>
<td>58 (26.6) [20.9-33.0]</td>
</tr>
<tr>
<td>Disease control rate (DCR) (ORR + stable disease) [95% Confidence interval]</td>
<td>17 (65.4) [44.3-82.8]</td>
<td>20 (69.0) [49.2-84.7]</td>
<td>48 (69.6) [57.3-80.1]</td>
<td>22 (84.6) [65.1-95.6]</td>
<td>143 (65.6) [58.9-71.9]</td>
</tr>
<tr>
<td>Time to progression (TTP), median (months) [95% Confidence interval]</td>
<td>7.8 [4-9-NR]</td>
<td>6.9 [4-2-11.2]</td>
<td>6.8 [3.4-10.2]</td>
<td>8.3 [5.5-11.4]</td>
<td>5.9 [4.9-8.1]</td>
</tr>
<tr>
<td>Overall survival (OS), median (months) [95% Confidence interval]</td>
<td>20.3 [9.6-NR]</td>
<td>27.3 [9.2-NR]</td>
<td>22.5 [19.0-NR]</td>
<td>20.0 [18.2-23.6]</td>
<td>21.3 [18.8-24.3]</td>
</tr>
<tr>
<td>Growth modulation index (GMI), median Range (min-max) &lt;1.1, n (%) &gt;1.1-&lt;1.33, n (%) ≥1.33, n (%)</td>
<td>0.7 (0.1-16.3) 15 (65.2)</td>
<td>0.9 (0.0-15.0) 12 (50.0)</td>
<td>0.7 (0.0-16.7) 35 (62.5)</td>
<td>3.0 (3.0-15.4) 11 (42.3)</td>
<td>0.8 (0.0-42.5) 10 (5.1) 76 (38.8)</td>
</tr>
</tbody>
</table>

*The GMI (TTP trabectedin/TTP prior chemo) was assessed on 196 patient: France, n
¼ 26; Germany, n
¼ 29; Italy, n
¼ 69; UK, n
¼ 26. NR, not reached.

and separately in countries with the highest recruiting rate to cover inter-country vari-
ations: France (F), Germany (G), Italy (I) and the UK.

Results: A total of 218 patients from 41 centers and 9 European countries were eval-
uated. Demographics and baseline characteristics of patients recruited in the 4 coun-
tries of interest were well-balanced and comparable to those observed in OP. Patients
received a median of 6 cycles of T (range: 1-44), mostly on an outpatient basis (n
¼ 132; 60.6%). Across all centers the median cycle duration, and median dose and dose intensity
were similar to those observed in OP. Analysis of PFS data showed a similar out-
come in G (median PFS: 5.9 months) to that observed in OP (5.9 months), and a rather higher PFS in the UK (8.3 months), F (7.6 months) and I (6.8 months). The patients
from the UK received the highest median number of cycles (18.5) and cumulative dose of T (26.2 mg) as compared to F, G and I. This was associated with favorable efficacy outcomes in those patients, particularly in terms of improved PFS (8.3 months), re-
sponses (ORR: 38.5%; DCR: 84.6%) and a high growth modulation index of 2.3. T treatment resulted in a comparable median overall survival in all patients (21.3 months), being somewhat larger among patients treated in sites across G (27.3 months). Febrile neutropenia (2.3% of patients), neutropenia, nausea, and pneumonia (1.4% each) were the most common T-related grade 3/4 adverse drug reactions.

Conclusions: In real-life setting T confers meaningful benefits to patients with multiple STS histotypes with a manageable safety profile regardless of small country variations. Clinical trial identification: Y-IMAGE, ET-D-020-12
Legal entity responsible for the study: PharmaMar
Funding: PharmaMar
Disclosure: C. Benson: Honoraria from PharmaMar for speaking and travel grants. B. Kasper: Honoraria from PharmaMar. All other authors have declared no conflicts of interest.

Safety and efficacy of pazopanib (PAZ) in advanced soft tissue carcinos (aSTS) by prior lines of therapy, age, and dose modifications: PALLETTE subgroup analyses

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2Department of Medical Oncology, University Hospital Essen Westdeutsches Tumorzentrum, Essen, Germany, Center for Sarcoma and Bone Oncology, DanaFarber Cancer Institute and Ludwig Center, Harvard Medical School, Boston, MA, USA,
3Sarcoma Unit, The Institute of Cancer Research and the Royal Marsden Hospital, Sutton, UK
4Novartis Oncology, Novartis Pharmaceuticals, East Hanover, NJ, USA
5Medical Oncology, Leiden University Medical Center (LUMC), Leiden, Netherlands

Background: PALETTE was a randomized phase 3 trial (NCT00735688) that demon-
strated single-agent activity of PAZ in advanced STS (aSTS). We evaluated the relation-
ship between age, prior lines of therapy, and dose modifications on the safety and
efficacy of PAZ in aSTS.

Methods: Median progression-free survival (mPFS) was evaluated in subgroups of prior lines of therapy (1 prior line; 2 or prior lines), age (<65 y, ≥65 y), and dose reduc-
tions and interruptions (no dose reduction/interruption; ≥1 dose reduction/interruption). Adverse events (AEs) were also compared in subgroups of prior lines of therapy and age. All analyses were descriptive and exploratory and require cautious interpretation.

Results: A total of 246 patients received pazopanib in the PALETTE study. Median PFS and median overall survival (OS) were longer in patients receiving PAZ who had only 1 prior line of therapy vs 2; prior lines of therapy (mPFS: 24.7 vs 18.9 weeks [Table]; OS: 13.7 vs 11.3 months). In patients receiving PAZ, mPFS was similar in ages <65 y and ≥65 y (20.0 and 20.1 weeks, respectively). In patients receiving PAZ, mPFS was maintained in patients requiring dose reductions or dose interruptions to manage toxicities.
Annals of Oncology

**Table 1501P**

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>N</th>
<th>Pazopanib, mPFS, weeks (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 prior line</td>
<td>110</td>
<td>24.7 (19.6-27.4)</td>
</tr>
<tr>
<td>2+ prior lines</td>
<td>136</td>
<td>18.9 (11.9-20.1)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 y (range: 18-64)</td>
<td>184</td>
<td>20.0 (17.9-22.0)</td>
</tr>
<tr>
<td>≥65 y (range: 65-85)</td>
<td>62</td>
<td>20.1 (11.7-31.6)</td>
</tr>
<tr>
<td>Dose reduction</td>
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</tr>
<tr>
<td>No dose reduction</td>
<td>154</td>
<td>11.9 (8.9-19.3)</td>
</tr>
<tr>
<td>≥1 dose reduction</td>
<td>92</td>
<td>27.7 (21.1-35.7)</td>
</tr>
<tr>
<td>Dose interruption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No dose interruption</td>
<td>107</td>
<td>11.0 (8.1-19.3)</td>
</tr>
<tr>
<td>≥1 dose interruption</td>
<td>139</td>
<td>21.5 (20.1-27.7)</td>
</tr>
</tbody>
</table>

mPFS, median progression-free survival; CI, confidence interval

Conclusions: Longer mPFS was observed in patients receiving PAZ following only 1 line of therapy. Additionally, mPFS with PAZ was maintained regardless of patient age or if dose modification was required to manage toxicity.

Clinical trial identification: NCT0073688

Legal entity responsible for the study: Novartis Pharmaceutical Corporation

Funding: Novartis Pharmaceutical Corporation


**1502P**

**Evolution in neutrophil-to-lymphocyte ratio (NLR) among advanced soft tissue sarcoma (STS) patients treated with pazopanib within EORTC 62043/62072 trials**

E. De Maio1, N. Touati2, S. Litie`re3, S. Sleijfer4, W.T.A. van der Graaf5, A. Le Cesne6, H. Geiderblom1

1Department of Medical Oncology, Institute Bergonie´, Bordeaux, France, 2Department of Medical Oncology, Gustave Roussy Cancer Campus, Villejuif, France, 3Department of Medical Oncology, Centre Leon Berard, Lyon, France, 4Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France, 5Department of Medicine, Institut Gustave Roussy, Villejuif, France, 6Department of Medicine, Institut Gustave Roussy, Villejuif, France

Background: Growth Modulation Index (GMI) has been used to define resistance to treatment with anti-VEGFR targeted agents, as patients with high GMI may respond to treatment and those with low GMI may experience rapid disease progression. Due to the lack of cross-resistance to targeted agents, GMI can be used to identify patients for whom switching to another TKI may be beneficial. The evolution of GMI during treatment with pazopanib was analyzed in the EORTC 62043/62072 trials.

Methods: Patients who received at least one TKI during their treatment were analyzed. GMI, defined as the ratio of TTP under TKI2/TTP under TKI1, was calculated. The median GMI was 0.76 (0.02 - 12.49). GMI was higher in the 40% with baseline. Compared with no changes, an increase or decrease in GMI did not impact the result and no association between changes in NLR and outcome was seen in placebo-treated patients. The median NLR change in patients treated with pazopanib was a decrease of 50.4% compared to an increase of 14.3% in placebo.

Conclusions: In this study, limited by its retrospective design, the prognostic value of NLR at baseline was confirmed in advanced STS patients, irrespective of treatment. Changes in NLR during the first 50 days of treatment with pazopanib were not associated with patient outcome and can therefore not be used as an early marker for response.

Legal entity responsible for the study: EORTC

Funding: EORTC-STEBSG

Disclosure: A. Le Cène: Pfizer, Lilly, Amgen, Novartis, Pharmamar Honoraria, myself, compensated. P.G. Casali: Consultant/Advisor, Honoraria and Research funds (for the institution) from Amgen, Dompé, Bayer, Blueprint Medicines, Eisai, Eli Lilly, Daichi Sankyo Pharma, Ipsynyme Inc., Merck KD, Merck Serono, NkTara Therapeutics, Novartis, Pfizer and PharmAmar. All other authors have declared no conflicts of interest.

**1503P**

**Benefit of the use of tyrosine kinase inhibitors (TKIs) in patients (pts) with METAsatic Soft Tissue SARComa (STS) in a Real-Life Setting: an ancillary analysis of the METASARC Study**


1Medical Oncology, Institute Bergonie´, Bordeaux, France, 2Department of Epidemiology and Clinical Research, Institut Bergonie´ Regional Cancer Institute of Bordeaux, Bordeaux, France, 3Department of Medical Oncology, Gustave Roussy Cancer Campus, Villejuif, France, 4Medical Oncology, Centre Leon Berard, Lyon, France, 5Medical Oncology, Leor Berard Center, Lyon, France, 6Department of Pathology, Institut Gustave Roussy, Villejuif, France, 7Biopathology, Centre Leon Berard, Lyon, France, 8Surgery, Institut Bergonie´, Bordeaux, France, 9Surgery, Institut Gustave Roussy, Villejuif, France, 10Radiology, Institut Bergonie´, Bordeaux, France, 11Radiation Oncology, Institut Gustave Roussy, Villejuif, France, 12Clinical and Epidemiological Research Unit, Institut Bergonie´, Bordeaux, France, 13Pathology, Institut Bergonie´, Bordeaux, France

Background: Treatment options for pts with advanced STS are limited. STS, like other proliferating malignancies, are dependent on the formation of new blood vessels to support their growth, invasion and metastasis. Growth Modulation Index (GMI) has been demonstrated as a relevant endpoint to assess clinical in patients with advanced STS. There are no data related to GMI in STS patients treated with anti-VEGFR targeted therapy.

Methods: Pts with metastatic STSs diagnosed between 1990 and 2013 and documented in the prospectively maintained database of the French Soft Sarcoma Group who have received at least one TKI during their treatment were analyzed. GMI, defined as the ratio of the Time To Progression (TTP) under the TKI/TTP under the previous line of treatment (TTP1) was calculated.

Results: 209 pts (102 male) were included in this study. Median age was 50 (11-83). Thresholds other than 40% did not impact the result and no association between NLR changes and outcome was seen in placebo-treated patients. The median NLR change in patients treated with pazopanib was a decrease of 50.4% compared to an increase of 14.3% in placebo.

Conclusions: In this study, limited by its retrospective design, the prognostic value of NLR at baseline was confirmed in advanced STS patients, irrespective of treatment. Changes in NLR during the first 50 days of treatment with pazopanib were not associated with patient outcome and can therefore not be used as an early marker for response.

Legal entity responsible for the study: French Sarcoma Group

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Alveolar soft part sarcoma (ASPS) is a rare entity. We present our experience with advanced ASPS treated with apatinib, a tyrosine kinase inhibitor directed against angiogenesis pathways.

Background: The clinical information of 6 patients with advanced ASPS who received apatinib treatment was 10.2 months (range, 1–21 months). Five of 6 patients who received at least 1 complete cycle of apatinib treatment were eligible for the efficacy analysis (Table). One patient achieved RECIST complete response. Apatinib treatment after six cycles. Four patients got partial response. No disease progression was found. The current objective response rate to apatinib treatment was 100% (5/5). The most common grade 3/4 treatment-related AEs were hand-foot syndrome (60.0%), hypertension (20.0%), and hepatotoxicity (20.0%). No drug-related severe AEs occurred. At the time of analysis, all patients were still alive and five patients continued to receive apatinib.

Conclusions: Our analysis confirms the short-term efficacy and safety of apatinib in patients with advanced ASPS. This result supports future randomized controlled trial to further verify anti-tumor activity of apatinib in stage IV sarcomas.

Legal entity responsible for the study: Chongqi Tu
Funding: None
Disclosure: All authors have declared no conflicts of interest.
Clinical Division of Oncology, Medizinische Universitaet Wien (Medical University of Vienna), Vienna, Austria, 2Department of Pathology, Medizinische Universitaet Wien (Medical University of Vienna), Vienna, Austria

**Background:** Treatment options in locally advanced/metastatic BS and STS are limited. PEM has shown first signs of promising activity in some histologic subtypes. In this named patient use of BS and STS patients who either failed standard therapy or where no standard therapy was established were treated with PEM. Results: 10 pts. were female (56%), 8 pts. male (44%). Median age was 45 yrs. (range 18-84 yrs.). Extent of disease at initial diagnosis was localized in 15 pts. (83%) and advanced/metastatic in 3 pts. (17%). The median number of previous lines of systemic treatment before PEM was 3 (range 0-7 lines). In total, 71 cycles of PEM were administered (median 3 cycles per pt., range 1-11 cycles). Immune-related side effects were infrequent.

**Methods:** This retrospective analysis includes efficacy/safety data from 18 pts. with advanced/metastatic BS/STS treated with PEM 200mg d1, q21d between May 2016 and April 2017.

**Results:** 10 pts. were female (56%), 8 pts. male (44%). Median age was 45 yrs. (range 18-84 yrs.). Extent of disease at initial diagnosis was localized in 15 pts. (83%) and advanced/metastatic in 3 pts. (17%). The median number of previous lines of systemic treatment before PEM was 3 (range 0-7 lines). In total, 71 cycles of PEM were administered (median 3 cycles per pt., range 1-11 cycles). Immune-related side effects were infrequent in two pts. and uveitis in one pt. PD-L1 assessment on tumor samples is ongoing.

**Abbreviation:** OSA = osteosarcoma, EMC = extraskeletal myxoid chondrosarcoma, LPS = liposarcoma, status 0 = alive, * = dead, status PEM 0 = PEM ongoing, 1 = PEM discontinued to PD (progressive disease), NED = no evidence of disease, PR = partial remission, SD = stable disease, ie = in response in evaluation.

**Table: 1507P**

<table>
<thead>
<tr>
<th>patient ID</th>
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<th>status PEM</th>
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<td>*</td>
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<td>11</td>
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<td>0 NED</td>
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<tr>
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<td>1</td>
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<td>0</td>
<td>0 PR</td>
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<tr>
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<td>2</td>
<td>*</td>
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<td>0</td>
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<td>dedifferentiated LPS</td>
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<td>0</td>
<td>0 PR</td>
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<td>0</td>
<td>0 SD</td>
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<td>0</td>
<td>0 PR</td>
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<tr>
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<td>angiosarcoma</td>
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<tr>
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<td>dedifferentiated LPS</td>
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<td>0 SD</td>
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<tr>
<td>18</td>
<td>myxoid LPS</td>
<td>2</td>
<td>0</td>
<td>0 ie</td>
</tr>
</tbody>
</table>

**Conclusions:** In this unselected cohort, PEM seems to have some activity in advanced/metastatic BS/STS. However, longer follow up of treated patients and prospective clinical trials of PEM in BS/STS patients will define the value of PEM in this patient cohort. Updated efficacy and toxicity data as well as PD-L1 expression levels will be presented at the meeting.

Thomas Brodowicz, Clinical Division of Oncology, Medical University of Vienna

**Disclosure:** None

**All authors have declared no conflicts of interest.

**Background:** Recent breakthroughs regarding the oncogenesis of gastrointestinal stromal tumor (GIST) have led to the wider use of imatinib (IM). In addition, since perioperative IM has been established, more accurate information regarding the clinical behavior of GIST is mandatory. However, there is no big data about the clinicopathological characteristics and prognosis of GIST in Japan. The aim of this study was to clarify them based on an analysis of the GIST registry conducted by the Kinki GIST Study Group in Japan.

**Methods:** The registry was designed to collect data on background characteristics, treatment methods, pathologic characteristics, and prognosis of primary GIST from 2003 through 2007 at 40 participating institutions.

**Results:** The study enrolled 346 male patients and 332 female patients. The median [range] age was 66 [18-95] yrs. The primary sites were stomach (74%), small intestine (19%), rectum (3%), esophagus (1%), colon (1%), and others (1%). Fifty-eight percent were asymptomatic and 42% were symptomatic e.g. bleeding (13%), pain (10%), and digestive symptoms (9%). None of the patients was received perioperative IM therapy.

**Pathological examination revealed that the tumor size was 4.0 [0.1-35] cm and the mitotic count was 3 [0-300] per 50 high-powered fields. There were 91.0% KIT positive GISTs and 82.9% CD117 positive GISTs. Ninety-seven (14.3%) patients showed recurrence and the common recurrent sites were liver (n = 58) and peritoneum (n = 33). According to the modified-Fletcher criteria, the recurrence rates were 0% (0/93, very low-risk group), 2.6% (6/230, low-risk,), 4.6% (4/87, intermediate-risk), and 38.9% (75/193, high-risk), respectively. The 5-years overall survival rate was 89.0%. The 5-years recurrent free survival rate (RFS) of gastric GISTs was significantly better than that of other sites. GISTs (5-years RFS 82.7% vs. 63.9%, P < 0.001).

**Conclusions:** We reported the clinicopathological characteristics of GIST in multicenter registry study in Japan. Currently applied GIST risk classification system is comparable to predict high- or low-risk patients with primary non-metastatic and completely resected GIST in pre-IM era.

**Legal entity responsible for the study:** Kinki GIST registry

**Funding:** Kinki GIST registry

**Disclosure:** All authors have declared no conflicts of interest.

**Background:** Pembrolizumab (PEM) in patients with advanced/metastatic bone sarcoma (BS) or soft tissue sarcoma (STS): Named patient use by the Medical University of Vienna

S. Schuh1, T. Brodowicz2, B. Gad1, H. Hamacher1, G. Amann2, S. Lang2

1Clinical Division of Oncology, Medizinische Universitaet Wien (Medical University of Vienna), Vienna, Austria, 2Department of Pathology, Medizinische Universitaet Wien (Medical University of Vienna), Vienna, Austria

**Background:** Treatment options in locally advanced/metastatic BS and STS are limited. PEM has shown first signs of promising activity in some histologic subtypes. In this named patient use of BS and STS patients who either failed standard therapy or where no standard therapy was established were treated with PEM.

**Methods:** This retrospective analysis includes efficacy/safety data from 18 pts. with advanced/metastatic BS/STS treated with PEM 200mg d1, q21d between May 2016 and April 2017.

**Results:** 10 pts. were female (56%), 8 pts. male (44%). Median age was 45 yrs. (range 18-84 yrs.). Extent of disease at initial diagnosis was localized in 15 pts. (83%) and advanced/metastatic in 3 pts. (17%). The median number of previous lines of systemic treatment before PEM was 3 (range 0-7 lines). In total, 71 cycles of PEM were administered (median 3 cycles per pt., range 1-11 cycles). Immune-related side effects were infrequent in two pts. and uveitis in one pt. PD-L1 assessment on tumor samples is ongoing.

**Abbreviation:** OSA = osteosarcoma, EMC = extraskeletal myxoid chondrosarcoma, LPS = liposarcoma, status 0 = alive, * = dead, status PEM 0 = PEM ongoing, 1 = PEM discontinued to PD (progressive disease), NED = no evidence of disease, PR = partial remission, SD = stable disease, ie = in response in evaluation.

**Table:**

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**Conclusions:** Based on this study, PD-L1-directed therapy may represent a particular opportunity for angiosarcomas of the skin given the frequency of PD-L1 expression and infiltration of immune cells. Our findings suggest prospective immunotherapy studies in this sarcoma subtype.

**Legal entity responsible for the study:** Department of Medical Oncology, West German Cancer Center, University Hospital Essen, University of Duisburg-Essen, Essen, Germany

**Disclosure:** None
Continuous TKI therapy appears to be important primarily for the prog-

Results: Seventy FDG-PETs for early response evaluation in 63 patients treated with neo-adjuvant intent were identified. Forty-one patients (63.1%) had a KiT exon 11 and 22 (34.9%) had a non-KiT exon 11 mutation (15 other and 7 unknown mutations). Of the 70 scans 64 (87.1%) had a baseline, 50 (71.5%) showed metabolic response (partial and complete), and 18 (25.7%) led to change in management. Change in management was strongly correlated with a lack of response (p<0.001) and a non-KiT exon 11 mu-
tation (p<0.001). PFS had a strong trend towards being shorter in patients with KiT exon 11 mutations (22.4 vs 58.2 months, p=0.09). Median PFS ranged from 22.4 months in the ST group to 63.6 months in the DT group.

Conclusions: In contrast to GIST patients harboring a KiT exon 11 mutation, in non-KiT exon 11 mutated GISTs treated with neoadjuvant intent early response evaluation by FDG-PET often leads to change in management. Legal entity responsible for the study: Neelhi Steeghs

Funding: Novartis, Pfizer and Bayer

Disclosure: N. Steeghs: Research grant for the Dutch GIST Registry from Novartis, Pfizer and Bayer. All other authors have declared no conflicts of interest.

Background: Gastrointestinal stromal tumors (GISTs) are the most frequent mesen-
chymal tumors of the gastrointestinal tract. Surgery is the method of choice in treat-
ment of localized GISTs but it also plays a great role in the treatment of advanced forms. The aim of our study is to define the role of surgery for locally advanced and metastatic/recurrent lesions.

Methods: We have performed a retrospective analysis from a prospectively docu-
mented database. All histologically proven GISTs, diagnosed and treated between 2003 and 2016, were enrolled from 4 clinics in Saint-Petersburg, Russia. Cases of recurrent or metastatic GISTs were selected from the registry, and baseline characteristics and survival outcomes were analyzed. Patients were classified into two groups. The surgical treatment group (ST group) included those who underwent surgical treatment in addi-
tion to tyrosine kinase inhibitor (TKI) therapy after recurrence or metastasis, whereas the drug treatment group (DT group) included those who were treated only with TKI therapy.

Results: Metastasis or recurrence developed in 34 (22.8%) of the 149 patients with GISTs who had undergone surgery for primary localized or locally advanced tumors, 13 (36.2%) of whom were assigned to the ST group and 21 (61.8%) to the DT group. Median follow-up was 68 (4-162) months. In the ST group the 3-year overall survival was 78.2% and the median TTP was 36.3 months. In the DT group the 3-year overall survival was 69.8% and the median TTP was 21.1 months. In univariate analysis, the following factors were associated with shorter TTP and OS: mitotic count (5.5 vs 15 per 50HPF, p=0.005), tumoral PDGFRA alteration (p=0.001), and primary tumors were bigger (10.4 vs 9 cm, p=0.0005) but had lower KiT exon 11 mutated count (5.5 vs 15 per 50HPF, p=0.005). There were no differences in terms of primary tumor location, disease status or metastases location at diagnosis. Multinomial profile from IM-LTR (KIT ex 11, 81%; KIT ex 9, 0%; PDGFRA, 8%; wild-type, 11%) did not differ significantly from CC. IM-LTR had significantly better response pattern (complete response 34.1%; partial response 43.9%; stable disease 22%) and overall sur-
vival (not reached) compared with CC (19.2%, 40%, 26.2%, and 63 months, respectively). Only 7 pts (18%) receiving IM for >5 years withdrew IM due to progression (69% CC, p<0.001). Eight pts (25%) developed ≥1 new metastases after ≥5 years on continuous IM, only 1 pt withdrew IM due to toxicity (grade 3 anemia). Univariate analyses show that pts with better PS (p=0.002), low mitotic count (p=0.003), low number of metastases (p=0.001), and better response to IM (p<0.001) achieve durable benefit from frontline IM.

Conclusions: Clinical and inherently biological tumor characteristics define a subset of GIST pts with increased likelihood to achieve durable benefit from IM. Molecular stud-
ies are needed to better identify these pts at treatment initiation.

Legal entity responsible for the study: Spanish Group of Sarcoma Research (GES)

Funding: Spanish Group of Sarcoma Research (GES)

Disclosure: All authors have declared no conflicts of interest.

Background: IM achieves disease control in most metastatic GIST pts, typically about 18 months. Interestingly, ~15% GIST pts remain on IM beyond 5 years of continuous treatment. To date, clinicopathologic features predictive of long-term benefit to IM re-
main largely unknown.

Methods: We analyzed clinical, pathological and molecular characteristics, and long-
term outcomes in metastatic GIST pts treated with continuous daily dosing of frontline IM in a cohort of pts benefiting ≥5 years, compared with a control group obtained from a national GES database.

Results: We found 41 IM long-term responders (IM-LTR) and 71 control cases (CC) with a median time on IM of 90.6 and 18.2 months, respectively. Compared to CC, IM-LTR were younger (59 vs 64 years, p=0.04), fitter at diagnosis (performance status (PS) 0-1: 100% vs 82.2%, p=0.001), had fewer metastasis prior to IM initiation (2.6 vs 7.5, p=0.001), and primary tumors were bigger (10.4 vs 9 cm, p=0.0005) but had lower KiT exon 11 mutated count (5.5 vs 15 per 50HPF, p=0.005). There were no differences in terms of primary tumor location, disease status or metastases location at diagnosis. Multinomial profile from IM-LTR (KIT ex 11, 81%; KIT ex 9, 0%; PDGFRA, 8%; wild-type, 11%) did not differ significantly from CC. IM-LTR had significantly better response pattern (complete response 34.1%; partial response 43.9%; stable disease 22%) and overall sur-
vival (not reached) compared with CC (19.2%, 40%, 26.2%, and 63 months, respectively). Only 7 pts (18%) receiving IM for ≥5 years withdrew IM due to progression (69% CC, p<0.001). Eight pts (25%) developed ≥1 new metastases after ≥5 years on continuous IM, only 1 pt withdrew IM due to toxicity (grade 3 anemia). Univariate analyses show that pts with better PS (p=0.002), low mitotic count (p=0.003), low number of metastases (p=0.001), and better response to IM (p<0.001) achieve durable benefit from frontline IM.

Conclusions: Clinical and inherently biological tumor characteristics define a subset of GIST pts with increased likelihood to achieve durable benefit from IM. Molecular stud-
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Legal entity responsible for the study: Spanish Group of Sarcoma Research (GES)

Funding: Spanish Group of Sarcoma Research (GES)

Disclosure: All authors have declared no conflicts of interest.

Background: In the randomized, controlled phase 3 GRID trial (NCT01271712), regorafenib (REG) significantly improved PFS versus placebo (PBO) in patients with advanced GIST (HR 0.268, P<0.001). Here we report an analysis exploring prognos-
tic characteristics of early tumor growth rate (eTGR) for PFS and OS.

Methods: The primary endpoint of GRID was PFS; OS was a secondary endpoint. Target lesions were assessed by central radiologic review based on RECIST (v1.1). Changes in target lesions over time were approximated by a parabola-like 3-parametric model. eTGR was defined as the percentage change per month of the sum of target le-
sion diameters from the start of double-blind treatment. To explore the association be-
 tween eTGR and PFS and OS, values of eTGR were split into quartiles (Q) separately by treatment arm. PFS (cut-off in 2012) and OS (cut-off in 2015) were compared in each subgroup population by median times derived from Kaplan–Meier curves and from modeling with a Weibull distribution.

Results: For PBO and REG, there is a nearly inverse relationship between eTGR and median times of PFS and OS from Q1 to Q4 for TGR. For the REG subgroup in Q1 eTGR, this trend is lost, as it is similar or worse median times than the subgroups around zero eTGR, which show the best prognosis.
**Background:** Deregulation of microRNAs (miRNAs) expression is observed virtually in all major types of neoplasm and miRNAs level in blood circulation are investigated as a potential diagnostics or prognostics biomarkers for neoplastic disorders. Gastrointestinal stromal tumors (GISTs) is the most common sarcoma of the gastrointestinal tract and to date performed studies on GISTs have provided mounting evidence on altered miRNA association with clinical, pathological features and Imatinib resistance in GIST. However, the utility of circulating miRNA as response markers of GIST progression and for Imatinib treatment have not been evaluated.

**Methods:** 36 metastatic or unresectable CD-117-positive GIST patients, were enrolled and serum sample was collected prior to Imatinib treatment. All patients responded initially to Imatinib therapy. In 12 patients an additional serum sample was collected following targeted treatment at the time of remission. Control group comprised 30 healthy individuals. MiRNAs were isolated from serum with MirVANA miRNA Isolation Kit and then analyzed using deep sequencing on Ion Torrent PGM. Reads were mapped to miRBase miRNA collection with miRDeep2. Differential expression was evaluated with edger.

**Results:** Deep sequencing identified 1284 miRNAs. The pair-wise comparison between Imatinib treated and Imatinib-naive GIST samples uncovered 22 miRNAs with differential expression (adjusted p-value < 0.05) of which 10 (miR-142-5p, miR-74a-3p, miR-233-5p, miR-233-3p, miR-125a-5p, miR-199b-5p, miR-24-2p, miR-641) yielded AUCCs (areas under Receiver Operating Characteristic curves) ranging 0.81 and 0.9, thus having a high discriminative properties. A comparison of imatinib-naive GIST and control healthy samples revealed 99 differentially expressed miRNAs (adjusted p-value < 0.001) of which four (miR-582-5p, miR-150-5p, miR-125a-5p, miR-125a-5p, miR-450b-5p, miR-450a-5p) reached AUCC with high discriminatory power ranging 0.81-0.84.

**Conclusions:** Circulating miRNA abundances can distinguish GIST patients from those in remission following Imatinib therapy as well as from the healthy controls.

However, further studies evaluating the potential of designated microRNAs as response markers for treatment or as predictive markers of GIST are warranted.

**Legal entity responsible for the study:** Piotr Rutkowski

**Funding:** the grant from National Science Center [2013/11/B/NS5/03165] to PR

**Disclosure:** All authors have declared no conflicts of interest.

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*By Weibull model of Kaplan–Meier curves; durations in months.

**1514P** Serum miRNA abundances discriminate imatinib-naive patients with advanced gastrointestinal stromal tumors (GIST) from those in remission on Imatinib therapy

H. Kosiela Paternici, A. Pacewska, M. Kuleckas, J. Karczmarzski, M. Dabrowska, A. Rosika, A. Balsas, M. Piatkowski, M. Mikuta, P. Rutkowski, J. Ostrowski

Soft tissue/Bone Sarcoma and Metanoma, The Maria Sklodowska-Curie Memorial Institute and Oncology Centre, Warsaw, Poland, Department of Gastroenterology, Hepatology and Clinical Oncology, Centre of Postgraduate Medical Education, Warsaw, Poland, Department of Genetics, The Maria Sklodowska-Curie Memorial Institute and Oncology Centre, Warsaw, Poland

**Conclusion:** miRNAs (adjusted p value < 0.01) of which four (miR-582-5p, miR-150-5p, miR-125a-5p, miR-125a-5p, miR-450b-5p, miR-450a-5p) reached AUCC with high discriminatory power ranging 0.81-0.84.

**Disclosure:** All authors have declared no conflicts of interest.

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<td><strong>LncRNA H19, HOTAIR and MALAT1 as prognostic molecular biomarkers in GIST</strong></td>
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<td><strong>N. Barraco1, L. Incorvaia1, G. Badalamenti1, F. Passigli1, A. Listi2, R. Maragliano2, E. Musso3, E. Bronte3, D. Cabibbi3, V. Calì3, M. Castiglia3, D. Fanale4, A. Galvano1, V. Grisina1, S. Ingrao2, L. Insalaco2, D. Massahra3, A. Perez1, V. Bazan2, A. Russo3</strong></td>
</tr>
<tr>
<td>1Department of Surgical, Oncological and Oral Sciences, Section of Medical Oncology, University of Palermo, Palermo, Italy, ADU Policlinico “Paolo Giaccone”, Palermo, Italy, 2Department of “Scienze per la Promozione della Salute e Materno Infantile “G.D’Alessandro”, University of Palermo, Palermo, Italy, ADU Policlinico “Paolo Giaccone”, Palermo, Italy, 3Department of Biomedicina Sperimentale e Neuroscienze Cliniche (BIONEC), University of Palermo, Palermo, Italy, ADU Policlinico “Paolo Giaccone”, Palermo, Italy</td>
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**Background:** Long non-coding RNAs (IncRNAs) are emerging as essential regulators of genetic and epigenetic networks. Their deregulation may underlie carcinogenesis supporting their potential involvement in tumorigenic and metastatic processes, as well as their role as prognostic/predictive biomarkers for clinical use in patients with several solid tumors. Few studies evaluated IncRNAs expression in rare tumors such as Gastrointestinal Stromal Tumours (GISTs). Here, the upregulation of HOTAIR has been associated with tumor aggressiveness and metastasis, and poor survival of GIST patients. In order to gain more detailed insight on the molecular role of IncRNAs, we analyzed the expression levels of IncRNAs H19, HOTAIR and H19 in tissue specimens of surgically resected GIST patients to evaluate the potential role of IncRNAs as prognostic biomarkers.

**Methods:** The expression of the IncRNAs H19, MALAT1 and HOTAIR has been evaluated in a total of 40 pairs of disease formalin-fixed paraffin-embedded tissue and adjacent normal tissue from 40 GIST patients with localized and locally advanced disease using quantitative real-time reverse transcriptase.

**Results:** H19 was overexpressed in 50% GIST patients (p-value: 0.0496). MALAT1 was overexpressed in 45% GIST patients (p-value: 0.032). None of them had the related date with HOTAIR. Furthermore, the up-regulation of H19 has been found in 74% patients harboring c-KIT mutations compared to 57% wild type patients (p-value: 0.042). Conversely the up-regulation of MALAT1 has been found in 76% patients harboring c-KIT mutations compared to 100% wild type patients (p-value: 0.027). Finally, the up-regulation of H19 has been found in 100% patients with TTP < 3 months compared to 25% patients with TTP > 3 months, while the up-regulation of MALAT1 has been found in 25% patients with TTP < 3 months compared to 75% patients with TTP > 3 months.

**Conclusions:** H19 and MALAT1 appear upregulated in GIST patients according to the KIT mutation status. These data would suggest a potential opposite prognostic value of both H19 and MALAT1 IncRNAs in these patients. The results of HOTAIR expression levels were indeterminate in all analyzed tumor samples, probably because HOTAIR has been degraded during its isolation. Further analyses are needed to confirm these data.

**Legal entity responsible for the study:** University of Palermo

**Funding:** None

**Disclosure:** All authors have declared no conflicts of interest.

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<td><strong>Predictive factors of response to Sunitinib in metastatic Gastrointestinal Stromal Tumors (mGISTs): A retrospective analysis</strong></td>
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<tr>
<td>L. Incorvaia1, G. Badalamenti1, F. Passigli1, A. Listi2, R. Maragliano2, E. Musso3, E. Bronte3, D. Cabibbi3, V. Calì3, M. Castiglia3, D. Fanale4, A. Galvano1, V. Grisina1, S. Ingrao2, L. Insalaco2, D. Massahra3, A. Perez1, V. Bazan2, A. Russo3</td>
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<td>1Department of Surgical, Oncological and Oral Sciences, Section of Medical Oncology, University of Palermo, Palermo, Italy, ADU Policlinico “Paolo Giaccone”, Palermo, Italy, 2Medical Oncology Unit, Campus Bio-Medica di Roma, Rome, Italy, 3Medical Oncology Unit, IRCCS istituto di Candido, Canale, Italy, 4Medical Oncology Unit, Policlinico S. Orsola-Malpighi, Bologna, Italy, 5Medical Oncology Unit, Policlinico Sant’Orsola Malpighi, Bologna, Italy</td>
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**Background:** Imatinib is currently the standard therapy for first line treatment of metastatic GIST. Although this treatment has demonstrated durable responses with PFS and OS benefit, most patients develop resistance and experience subsequent disease progression. Current treatment available in second line are Imatinib high-dose (800 mg/day) or Sunitinib. The presence of two options in this setting, in the absence of direct comparisons, raises many questions on the choice.

**Methods:** A total of 128 patients with metastatic GIST were collected in our analysis in this large database. We analyzed the validity of several parameters as possible predictors of response to treatment with Imatinib high-dose vs Sunitinib in patients progressing at the standard dose of Imatinib 400 mg/day. The parameters analyzed were: anatomic...
site of primary GIST, site of metastasis, KIT and PDGFRα mutational status, and FDG-PET status at progressing disease. Every factor has been correlated with Progression Free Survival (PFS) for Imatinib 800 mg/day and Sunifiram treatment, measured in months. Data collected have been analyzed with software “Medcalc”, performed by using the Kaplan-Meier method.

Results: Univariate analysis showed Sunifiram more active then Imatinib in gastric GISTs (median PFS: Sun 12 months vs Ima 800 6 months; p < 0.0001), in pts with peri- toneal metastasis (median PFS: Sun 10 months vs Ima 800 5 months; P = 0.0249), in wild-type (median PFS: Sun 20 months vs Ima 800 17 months; P = 0.1361) and PET-negative GIST patients (median PFS: Sun10 months vs Ima 800 7 months; P = 0.0874).

Conclusions: With the limitations of a retrospective analysis, this study identifies the gastric site of primary tumor as a predictive factor to efficacy of Sunifiram treatment in second line. The mutational status (GIST WT), the site of metastasis (peritoneum) and the FDG-PET status (negative), although not statistically significantly, seem to be elements of increased activity for Sunifiram treatment in second line.

Legal entity responsible for the study: University of Palermo

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Analysis of PD-L1 Expression in Patients with Gastrointestinal Stromal Tumors

A.B. Kinupe Abrahao 1, R. Jamani 2, E. Hsieh 3, Y-J. Ko 2

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Background: The immune system is believed to have an important role in solid tumor progression. The development of monoclonal antibodies targeting immune checkpoints, such as programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1), have revolutionized the treatment of some cancers. Recent efforts have attempted to elucidate the relevance of the PD-1/PD-L1 pathway in gastrointestinal stromal tumors (GIST).

Methods: Formalin-fixed, paraffin-embedded specimens were obtained from resected GIST at Sunnybrook Health Sciences Centre between March 2008 and August 2015. PD-L1 analysis was based off a tissue microarray of the cases using the Roche Ventana SP263 antibody. Each case had 1 mm cores taken from different areas of the tumor block. Normal controls used for PD-L1 were placenta and tonsil (epithelial and inflammatory).

CD117 was assessed via immunohistochemistry in all tumor specimens.

Results: Of twenty-nine patients who underwent surgical resection, eight had insufficient tumor tissue for analysis, and three cases were excluded due to CD117 negativity after preoperative imatinib treatment; leaving 18 patients for analysis. Three of these 18 cases were positive for PD-L1 expression: 2 patients with moderate PD-L1 staining in 85% of the stromal cells and 1 with weak staining in 15% of the stromal cells. Fifteen patients were negative for PD-L1 expression. Analysis of PD-L1 expression in tumor-infiltrating lymphocytes was not feasible due to the lack of inflammatory cells in tumor environment. The patients whose samples had significant PD-L1 expression had gastric primaries, with tumour size <10cm. They did not require preoperative treatment, and did not have metastatic disease despite two having a high mitotic rate. The clinicopathologic characteristics of patients by PD-L1 expression status is demonstrated in Table 1.

Legal entity responsible for the study: University of Palermo

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1519P Primary pleomorphic sarcoma (PS) and leiomyosarcoma (LMS) of bone: Retrospective analysis of an original series

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1Medical Oncology Unit, Nuovo Ospedale di Prato, Prato, Italy; 2Pathology Department, University of Florence, Florence, Italy; 3Orthopedics Oncology Department, Azienda Ospedaliera-Universitaria Careggi, Florence, Italy; 4Radiotheraphy Department, University of Florence, Florence, Italy; 5Radiology, Azienda Ospedaliera-Universitaria Careggi, Florence, Italy; 6Radiology Department, Azienda Ospedaliera-Universitaria Careggi, Florence, Italy; 7Sandra Pagliani Translational Research Unit, Nuovo Ospedale di Prato, Prato, Italy

Background: To describe the clinicopathological features of 23 patients affected by primary PS and LMS of bone, to confirm the diagnosis by molecular analysis, to evaluate the clinical outcome and to explore the prognostic impact of these features on disease-free (DFS) and overall survival (OS).

Methods: Primary PS and LMS of bone surgically treated from 2004 to 2015 were retrospectively reviewed. We analysed: age, sex, stage, histotype, histological grade and surgical and/or medical therapy. IDH1 mutational status was evaluated and immunohistochemical staining was performed for smooth muscle actin and desmin. For molecular analysis tumor DNA was extracted from freshly cut FFPE blocks by GeneReAtlas™ DNA FFPE (Quagen) and ddPCR (Bio-rad) was used to determine the presence of IDH1H and IDH1C mutations. DFS and OS rates were calculated according to the Kaplan-Meier method. The differentiation (myogenic, MD) versus non-myogenic, NMD) was correlated with the outcome using the Kaplan-Meier method.

Results: 23 patients with primary PS or LMS of bone were included in the study. Median age was 49 years (range 13-90), male/female 14/9, 18 had localized disease and 5 metastatic disease. 17 received surgery, 14 received adjuvant therapy, 5 received neo-adjuvant chemotherapy and 5 received up-front chemotherapy for advanced disease. All cases were histologically and radiologically reviewed: 17 PS and 6 LMS were identified. All cases were high-grade (FNCLCC grading system). Mutational analysis is currently underway and it will be presented at the meeting. 5-year OS of the whole series was 60% (95% CI, 3.1 – NE) and 5-year DFS was 50% (95% CI, 1.6 – 12.2). Patients with advanced disease were 13: 5-year OS in this subgroup was 38% (95% CI, 2.5 – NE). We identified MD in 11 cases. There were no significant differences between the MD and NMD groups in terms of DFS (logrank p-value=0.6788) and OS (logrank p-value=0.7589).

Conclusions: These primary malignant bone tumours are very rare with poor prognosis after relapse or when radical surgery is not feasible. MD did not predict a worse outcome than NMD in terms of OS and DFS.

Legal entity responsible for the study: Giacomo Giulio Baldi

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Background: HDMTX followed by calcium folinate (CF) rescue is established as part of MAP chemotherapy to manage toxicity during osteosarcoma treatment. A problem with HDTMX is the variability in plasma exposure of both MTX and CF leading to an unpredictable response. A potentially superior rescue agent methyleptheratydrololate (Modufolin®), containing the active metabolite of CF, has been evaluated to identify a safe and effective dose for further development.

Methods: This exploratory study performed in Hungary, Poland, Sweden and Czechia involved osteosarcoma patients, 12-40 years, planned for MAP chemotherapy. All patients received one MAP cycle (two HDMTX courses) with standard CF rescue of 15 mg/m². Those that completed this MAP cycle successfully according to six defined criteria subsequently received Modufolin® in the following two (HDMTX courses). There were two Modufolin® dose cohorts, 15 mg/m² (1) and 7.5 mg/m² (2). A Data and Safety Monitoring Board evaluated safety before initiation of the second dose cohort and suggested the dose for further development.

Results: Eight patients 12-17 years were included. Four patients were treated in cohort 1 and four in cohort 2. In cohort 1, no MTX toxicity or delayed elimination with subsequent treatment delay was reported. In cohort 2 one patient reported mucosal grade 3 and failed successful advancement after first course of Modufolin®. In both cohorts and after both types of rescue, there were cases with significantly increased s-creatinine levels.

Conclusions: Modufolin® seems to be a safe and effective rescue agent after HDMTX. The study design however precludes a comparison between Modufolin® and CF, since only patients with successful CF rescue received Modufolin®. The higher dose of 15 mg/m² seemed more effective as rescue and was selected for further development.

Clinical trial identification: EuRaCT Nr 2013-001280-23

Legal entity responsible for the study: Isolof Medical AB

Funding: Isolof Medical AB

Disclosure: All authors have declared no conflicts of interest.

1523P Efficacy of second line treatment with etoposide and ifosfamide in adult patients with advanced Ewing Sarcoma family tumors

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Background: Ewing Sarcoma family tumors (ES) are rare subtypes of sarcomas, and even less common in adult patients. For those not amenable to treatment with curative intent, sequential therapy with multi-agent combinations is the standard of care, usually followed by ifosfamide/etoposide (IE) at the time of progression, largely based on protocols that included pediatric patients. Nevertheless, less is known about the efficiency of this approach for adult patients with ES refractory to first-line therapy.

Methods: We assembled a retrospective cohort of patients aged 18 or older diagnosed with metastatic/inoperable ES refractory to first-line combinations, treated with IE between 2010 and 2016. Patient characteristics, tumor variables, treatment outcomes and toxicity data were evaluated. Kaplan-Meier method was used to estimate overall survival and uni/multivariate analysis were carried out to identify factors associated with survival.

Results: Among 18 adult patients, the mean age of diagnosis was 22 years, 73% were male and 84% had an ECOG of 0-1 at commencement of IE. Pelvis and thorax were the most common primary sites. The mean number of cycles of IE was 4. The disease control rate was 27%, with partial responses occurring in 16% of the patients (there were no complete responses). The median OS was 4.8 months (IC 95% 0.7-8.4). Toxicities grade 3 occurred in 61% of the patient, including two treatment-related deaths. The main grade 4 toxicity was febrile neutropenia. Hospitalization were required in 53% of the cases.

Conclusions: IE has limited efficacy and significant toxicity when used in the second-line setting for adult patients with advanced ES, and different approaches should be investigated for these patients.

Legal entity responsible for the study: Instituto do Câncer do Estado de São Paulo

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Background: Chondrosarcoma (CS) is the second most frequent primary malignant bone tumor in adults. Surgery is the best treatment option for these patients since most subtypes are resistant to chemotherapy and radiotherapy, thus novel systemic therapies are needed for patients with unresectable tumors. The majority of cases correspond to the conventional central CS histology, were recurrent mutations in isocitrate dehydrogenases (IDH1/2) coding genes are found. Therefore, IDH1 has been reported as a potential therapeutic target and several selective inhibitor molecules, such as AGI-5198 and, more recently, AG-120, have been developed and are currently being evaluated in clinical trials. In this work, we have explored the in vitro effects of AG-120 on a central CS cell line, JF012, which carries a mutation in IDH1.

Methods: JF012 cells were cultured both in monolayer and three-dimensional (3D) spheroids and treated with increasing concentrations of AG-120. IDH1 mutation in arginine residue R132G was verified by PCR sequencing. Proliferation and cytotoxic screening were done with Sulforhodamine B (SRB) assay. Monolayer invasion and migration assays were performed with FluoroBlok and wound healing assays respectively and 3D experiments were developed using a Matrigel matrix.

Results: R132G mutation of IDH1 was confirmed by PCR sequencing. Previous reports with AGI-5198 inhibitor show contradictory results regarding their effect on CS cells. In this work, we show how novel molecule AG-120 inhibits both invasion and migration of CS IDH1 mutated JF012 cell line in monolayer and 3D cell culture, although it does not affect their proliferation. Minor effects on viability were only detected at high dose (100 μM).

Conclusions: These results support AG-120 as a new possible therapeutic agent for patients with metastatic CS, and further research is needed to understand its action mechanisms in this pathology.

Legal entity responsible for the study: Fundación para la Investigación Biomédica del Hospital Universitario La Paz (FIBHULP)

Funding: Fundación para la Investigación Biomédica del Hospital Universitario La Paz (FIBHULP)

Disclosure: All authors have declared no conflicts of interest.
Background: The immune surveillance reactivator lefitolimod (MGN1703), a DNA-based TLR9 agonist, is currently in a comprehensive clinical development program including a phase 3 trial in mCRC. The phase 2 IMPULSE study was designed to evaluate the efficacy and safety of lefitolimod in small-cell lung cancer (SCLC).

Methods: IMPULSE is a randomized, international, multicenter, open-label trial to assess the effect of lefitolimod-mediated immune surveillance reactivation on overall survival (OS) in extensive-disease SCLC. 102 patients with objective tumor response following 4 cycles of platinum-based first-line induction therapy were randomized 3:2 to receive either lefitolimod maintenance therapy or local standard of care (control). Upon relapse, patients have received appropriate second-line therapy.

Results: Out of 102 patients, 61 were randomized to the lefitolimod, 41 to the control arm. Distribution of patients to the two arms was balanced regarding patient demographics. Even though in this highly challenging indication the primary endpoint OS of the overall study population was not met, IMPULSE showed positive results in two pre-defined, clinically relevant subgroups: (1) patients with CNS involvement and (2) patients with early disease (HR 0.54, 95%CI 0.29-1.21, n = 95). The most common treatment-related adverse events (AEs) were hematologic (G3-4 neutropenia/thrombocytopenia: L 62%, G4 neutropenia: 18%), increases in transaminases (G3/4 transaminases: L 11%, G4 transaminases: 0%), and G4 rash. Only 4 of 16 pts were discontinued due to AEs. As of May 1, 2017, 4 of the 16 pts evaluable for efficacy achieved partial responses (2 unconfirmed). Updated efficacy data as well as data from ongoing biomarker analyses will be presented.

Conclusions: BMS-986012 in combination with nivolumab is well tolerated in pts with rel/ref SCLC, with no evidence of additive toxicity. Promising initial antitumor activity was observed with BMS-986012 + nivolumab in pts with rel/ref SCLC. Clinical trial identification: NCT02247349

Legal entity responsible for the study: Bristol-Myers Squibb

Funding: Bristol-Myers Squibb

Disclosure: N.B. Leighl: Research funding (institution) - Novartis. Travel/honoraria (unrelated CME) - AstraZeneca, Pfizer, Bristol-Myers Squibb, Merck, Sharp & Dohme.


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All other authors have declared no conflicts of interest.

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Clinical trial identification: NCT01970740
Legal entity responsible for the study: PharmaMar SA
Funding: PharmaMar SA
Disclosure: M. Forster: Consulting or advisor or travel and accommodation in Lilly, Pfizer, BI, Novartis Merck, Astra Zeneca. E. Calvo: Speakers’ Bureau in Novartis and travel or accommodation expenses in Lilly, PsiOxus, Novartis. M.P. Lopez Criado: Relation with Lilly, Bristol Myers Squibb, accommodations with Bristol. J.A. Lopez-Vilarino de Ramos, X.E. Luepke-Estefan: Employee in PharmaMar. C. Kahatt, P. Lardelli, A. Soto-Matos: Employee and Stock in PharmaMar. All other authors have declared no conflicts of interest.

**1530PD**
Results of a randomized, placebo-controlled, phase 2 study of tarextumab (TRXT, anti-Notch2/3) in combination with etoposide and platinum (EP) in patients (pts) with untreated extensive-stage small-cell lung cancer (ED-SCLC)

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Background: Notch signaling is implicated in cancer stem cell biology and is an appealing target in the treatment of SCLC. TRXT, a fully human anti-Notch2 antibody, has shown preclinical efficacy in SCLC. A randomized phase 1b/2 study was conducted.

Methods: This was a randomized, placebo-controlled, multi-center study. Pts were randomized 1:1 to platinum (cisplatin 75 mg/m² or carboplatin AUC of 5 mg/ml*min on day 1, investigator’s choice) + etoposide (EP) 100 mg/m² on days 1-3 or TRXT 15 mg/kg on day 1 or EP + placebo (pbo) every 21 days. Chemotherapy was used for 6 cycles, and TRXT/ pbo was continued until disease progression. Primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), overall response rate (ORR), safety, and PFS/OS in 5 biomarker groups.

Results: 145 pts were enrolled (137 treated). Demographics and baseline pt characteristics were balanced between arms. PFS was similar between the treatment arms (median 10.3 mo in EP + pbo vs 9.3 mo in EP + TRXT, HR = 1.01, p = 0.89). ORR was 70.8% in EP + pbo vs 68.6% in EP + TRXT (p = 0.83). There were no statistically significant differences in OS or PFS according to Notch3, Hes1, Hey2, Hey1, or Hes6 gene expression levels. Adverse events (AE) were more common in EP + TRXT; most commonly increased drug-related AEs included diarrhea (33.8/76.8%), thrombocytopenia (17/63.8%), decreased appetite (23/53.7%), hypokalemia (7/43.3%), and vomiting (13/23.9%). Most commonly increased grade 3 or higher AEs in the EP + TRXT arm included thrombocytopenia (10/34.6%), anemia (20/67.7%), pneumonia (4/43.5%), diarrhea (10/18.9%), and hypokalemia (4/43.5%). AEs with fatal outcome were more common in EP + TRXT (4/4.8%).

Conclusions: Tarextumab in combination with platinum-based therapy did not improve PFS, OS, or ORR in previously untreated SCLC. Biomarker analysis failed to establish a predictive marker for TRXT efficacy. Pts treated with TRXT experienced more toxicity.

Clinical trial identification: NCT01859741
Legal entity responsible for the study: OncoMed Pharmaceuticals
Funding: OncoMed Pharmaceuticals
Disclosure: S.V. Liu: Consultant; Ariad, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Genentech, Lilly, Pfizer. A. Kapoun, L. Faoro: Employee and stock holder at OncoMed Pharmaceuticals. All other authors have declared no conflicts of interest.

**1531PD**
Clinical outcomes for EGFR-mutant adenocarcinomas (AC) that transform to small cell lung cancer (SCLC)

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Background: About 5-10% of EGFR-mutant lung ACs transform to SCLC at the time of acquired resistance. The clinical course of patients (pts) with this finding is poorly characterized.

Methods: We retrospectively reviewed the records of all 16 pts with EGFR-mutant SCLC that have been seen at our center under an IRB-approved protocol and summarized demographics, disease features, and clinical outcomes.

Results: Among 16 pts, 10 were women. 15 had AC histology at diagnosis; one had de novo SCLC with EGFR de novo. 11 were never-smokers. All but the de novo case received an EGFR tyrosine kinase inhibitor (TKI) prior to transformation (7 had >1 prior TKI; 6 received a 3rd-gen TKI) and 14/15 were on a TKI when the SCLC was noted. Median time from diagnosis to SCLC was 29.6 mo (95% CI 10.8-38.1). 15/16 of the SCLC tumors were genotyped; all kept their founder EGFR mutation and none had T790M, including 5 pts with prior T790M negativity. Not all samples were assessed for genotype by the same assay, though recurrent mutations observed in at least 25% of cases were T790M, PIK3CA and BRCA (full genetic data will be shown at meeting). The most common therapy given directly after SCLC diagnosis was platinum-etoposide (n = 9), all SCLC treatment lines considered, platinum-etoposide had a clinical response rate of 72% (8/11) and progression-free survival of 4.6 mo (95% CI 2.3-8.5). Seven pts also had a taxane at some point after the diagnosis of SCLC, and 4/7 (57%) responded. Median overall survival (mOS) from initial cancer diagnosis was 38.2 mo (95% CI 24.5-43.9) and mOS from time of SCLC diagnosis was 12.4 mo (95% CI 4.0-16.6).

Conclusions: EGFR-mutant ACs that transform to SCLC uniformly maintain their founder EGFR mutation and is mutually exclusive with T790M (though both can be observed sequentially). In our cohort, the median time from initial lung cancer diagnosis to transformation was 2.5 years. The mOS of 12.4 mo following diagnosis of SCLC is

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**Table: 1529PD**
Response Evaluable patients Lurbinectedin+DOX (q3wk) Lurbinectedin + TAX (q3wk) Lurbinectedin alone (q3wk)

<table>
<thead>
<tr>
<th>Cohort A</th>
<th>Cohort B</th>
</tr>
</thead>
<tbody>
<tr>
<td>L 3.5 mg</td>
<td>L 2 mg/m²</td>
</tr>
<tr>
<td>CR</td>
<td>PR</td>
</tr>
<tr>
<td>2 (10%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>12 (67%)</td>
<td>10 (37%)</td>
</tr>
<tr>
<td>3 (14%)</td>
<td>9 (33%)</td>
</tr>
<tr>
<td>4 (19%)</td>
<td>10 (33%)</td>
</tr>
<tr>
<td>17 (81%)</td>
<td>19 (70%)</td>
</tr>
</tbody>
</table>

CR, Complete Remission; PR, Partial Remission; ORR, overall response rate; SD, stable disease; PD, progressive disease; DCR, disease control rate; DOR, duration of response; FD, flat dose; D1, day 1; D18, day 18; CT, chemotherapy; TAX, taxane; CTFI, chemotherapy free interval.

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**Key points:**
- No statistically significant differences in OS or PFS according to Notch3.
- Tarextumab (TRXT, anti-Notch2/3) has shown preclinical efficacy in SCLC.
- A randomized phase 1b/2 study was conducted.
- Results of 145 pts were evaluated; 137 were treated.
- Demographics and baseline pt characteristics were balanced between arms.
- PFS was similar between the treatment arms.
- Adverse events (AE) were more common in EP + TRXT.
- Most commonly increased drug-related AEs included diarrhea, thrombocytopenia, decreased appetite, hypokalemia, and vomiting.
- AEs with fatal outcome were more common in EP + TRXT.

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**Keywords:**
- Notch signaling
- Small cell lung cancer (SCLC)
- EGFR-mutant adenocarcinomas
- Tarextumab
- Platinum-based therapy
- Progression-free survival
- Disease control rate
- Duration of response
similar to that seen among pts with non-EGFR-mutant SCLC. Likewise, responses to platinum- etoposide were frequent, but transient. 4 pts also responded to a taxane. Interestingly, mSOS from diagnosis was similar to expected mSOS for pts that never transitioned to SCLC at 38.2 mo. Further investigation is needed to better elucidate optimal strategies for this group.

Legal entity responsible for the study: Leica V Sequist

Funding: None

Disclosure: Z. Piotrowska: Advisory board/consulting honoraria from AstraZeneca, Boehringer Ingelheim and Ariad Pharmaceuticals. A.F. Farago: Consulting for Pharmacan, Abbvie, Takeda, Merrimack, Intervention Insights. Honorarium from Foundation Medicine. A.N. Hata: Amgen - consulting and research support Novartis - research support. L. Sequist: Consulting for AZ, Ariad, IMS and Genentech - and research supports from Clovis, AZ, BI, Novartis, Merrimack, Pfizer, Genentech, Merck, Johnson & Johnson. All other authors have declared no conflicts of interest.

1532P The role of thoracic radiotherapy on peripheral lymphocyte subsets in patients with limited-stage small cell lung cancer

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Background: Over the past decades, there has been a lack of significant breakthroughs in small cell lung cancer therapy, the current standard care is still concurrent chemoradia- tion. Recently, immune checkpoint inhibitors in anti-tumor clinical application has achieved remarkable results. There is evidence suggest that radiation and chemotherapy can alter the immune microenvironment, many clinical trials combing radiation and chemotherapy with checkpoint inhibitors are underway. But how chemotherapy or radiotherapy affects any existing anti-tumor immune response and how that response is changed following clinical treatment are still not elucidated fully. In this study, we investigated the changes of immune subsets in patients with LS-SCLC.

Methods: Blood samples were obtained from 48 patients before and after radiotherapy and 31 patients before and after induction chemotherapy. PBMCs were purified using standard Ficoll density gradient centrifugation. The percentage of circulating lympho- cytocyte subsets were measured by flow cytometry. Patient data include clinical characteristics, disease prognostic information, survival information etc. The SPSS 22.0 software was used for the data analysis.

Results: Among the 31 patients, most values of T-lymphocyte subsets showed no statistically significant difference before and after induction chemotherapy. Among the 48 patients, remarkable elevation of CD3+, CD8+ T cells were noticed, CD4+, CD56+, CD4+CD345RA+ and cells CD4+/CD8+ ratio were significantly decreased after radiotherapy. Then we further analyzed the changes of lymphocyte subsets in 17 patients be- fore and after induction chemotherapy as well as radiotherapy, which further confirmed the changes of immune subsets caused by radiotherapy but not induction chemotherapy.

Conclusions: This study suggest that thoracic radiotherapy but not induction chemo- therapy has an immunomodulatory effect on LS-SCLC patients, which provides new insights relevant for designing more optimal combination of immunotherapy in such cohort, especially for the appropriate time and sequence of immunotherapy, radiother- apy and chemotherapy.

Legal entity responsible for the study: Yamei Chen

Funding: National Natural Science Foundation of China

Disclosure: All authors have declared no conflicts of interest.

1534P Antidepressants simulate enriched environment enhance platinum chemosensitivity of small cell lung cancer

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Background: Small cell lung cancer (SCLC) is one of the most lethal malignancies with rapid chemoresistance. Numerous studies have been devoted to reversing chemoresis- tance. However, it is still far from successful with a clear way to reverse the effect of chemoresistance. Based on our previous study, enriched environment (EE) has a clear effect on improving the mental state of mice and can reduce chemotherapy resistance caused by platinum regimens. In this study we investigated the complex links between benign mental stress (EE) and chemosensitivity of SCLC, and use anti-depressants to improve the mental state of mice to observe its impact on chemosensitivity to platinum regimens, and the underlying mechanism was explored.

Methods: The mental state of mice was comprehensive evaluated by behavior tests in- clude elevated plus maze (EPM), open field experiment (OF), forced swimming (FS). Then, the mice were transplanted subcutaneously and treated with cisplatin, carbopla- tin and oxalaplatin. Tumor growth and the results of behavior test were analyzed. The tumor was analyzed by gene expression profiling and the differential genes were screened. The expression level of differential genes were examined by real-time PCR, and verified by western blot and immunohistochemistry, respectively. And then we exam- ined the effects of antitumor drugs inducing chemoresistance in NCI-H69 cell, and ABG2 blocker was used for chemosensitivity verification in vivo and in vitro.

Results: EE significantly increased the time of movement of the in the EPM (35.24 sec V.S. 16.78 sec, P < 0.01), increased the center area time in OF test (54.25 sec V.S. 35.24 sec, P < 0.05), significantly increased the struggling time in the FS test (46.02 sec V.S. 25.81 sec, P < 0.01). For antidepressants, it can also significantly improve the state of depression of mice, improve the behavior results, but can not achieve the effect of EE (EPM: 50.25 sec V.S. 35.24 sec; OF: 49.84 sec V.S. 54.25 sec; FS: 57.28 sec V.S. 46.02 sec). For platinum chemosensitivity test, the antidepressant drugs (Diazepam, Quetiapine and Clomipramine) without direct inhibition to NCI-H69 cells. Antidepressants and EE have significantly increased the sensitivity of chemoresistance in mice, but antidepress- sants can not achieve the inhibitory effect of EE. We detected the serum of mice and found that the serum BDNF levels significantly decreased in EE mice. Similarly, anti- depressants also significantly reduced serum BDNF levels in mice. Gene expression profiles showed that a variety of genes were downregulated in the tumor tissue of EE and antidepressants mice, mainly in ABC transporters and drug metabolic pathways. The expression level of ABCB1, ABCG2, ABCG3, ABCG8, PPARa, DPT, GST-P1 and GSTM1 in NSCLC sample were examined real-time PCR, and verified by western blot and immunohistochemistry, respectively. ABG2 expression in tumor of EE and anti- depressants mice were even 3-fold higher than control (P < 0.001), and the same results were obtained by WB and IHC verification. For platinum chemosensitivity test, EE significantly increased the sensitivity to platinum based drugs (P < 0.001).

Conclusions: Antidepressants can partially mimic the chemotherapeutic effect of EE and we confirm that the mechanism is partially achieved by increasing BDNF and reducing the expression of ABG2.

Legal entity responsible for the study: Henan Cancer Hospital

Funding: Research Foundation of Henan Cancer Hospital (nos. 2015511004 to Yufeng Wu)

Disclosure: All authors have declared no conflicts of interest.

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Annals of Oncology
Background: Small cell lung cancer (SCLC) is a chemoresistant malignancy with high response rates in early lines of therapy, but will inevitably recur. For patients (pts) with progressive SCLC following treatment with at least two prior therapies, standard treatment has not been established. Rovalpituzumab tesirine (Rova-T,™) is an antibody-drug conjugate that targets Delta-like protein 3 (DLL3), an atypical Notch receptor family ligand, and a marker specific for tumor-initiating cells in SCLC and other neuroendocrine tumors with little to no expression in normal tissue. Rova-T is a covalently linked humanized DLL3-specific IgG1 monoclonal antibody tethered to a toxic DNA cross-linking agent by a cleavable linker. Rova-T binds DLL3 on target-expressing cells, is internalized, and the toxin released to induce cell death. A Phase 1 study of Rova-T in SCLC demonstrated robust antitumor activity in DLL3-high pts and a manageable safety profile. The safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of Rova-T has not been evaluated in Japanese SCLC pts, thus a study of Rova-T in this population is warranted.

Trial design: This is a Phase 1, multicenter, Japanese, open-label dose escalation study (NCT03086239). Primary objective: to assess safety and tolerability of Rova-T in Japanese pts with advanced, recurrent SCLC. Secondary objectives: to explore antitumor activity of Rova-T, to study PK and pharmacodynamics of Rova-T. Pt eligibility: historically confirmed advanced, recurrent SCLC with measurable disease and documented disease progression after at least 2 prior systemic regimens, including at least 1 platinum-based regimen; ECOG 0-1; no prior exposure to a pyrrolobenzodiazepine-based drug. A standard 3 + 3 dose escalation will be used with ≤ 18 pts enrolled (6/dose level x 3 levels) and ≤ 60 pts if expansion cohorts are executed. Arm A: Rova-T 0.2, 0.3, or 0.4 mg/kg intravenously on Day -1, Day 1, and Day 2 of each 6-week cycle. Dose escalation will proceed until a single maximum tolerated dose (MTD) is determined (not to exceed 0.4 mg/kg). L. Rudin et al., Lancet Oncol, 2016.

Clinical trial identification: NCT03086239

Legal entity responsible for the study: AbbVie Scentrx

Funding: AbbVie Scentrx

Disclosure: I. Okamoto, H. Udagawa, S. Kanda, M. Takeda, H. Akamatsu: Serves as an investigator for Abbvie Scentrx. T.H. Han, I. Lakatos, F. Zhang, C. Scripture: Employee of AbbVie Scentrx and may own AbbVie stock. S. Okubo: Employee of AbbVie and may own AbbVie stock. All other authors have declared no conflicts of interest.

A phase 1/2 study on safety of rovalpituzumab tesirine in combination with nivolumab or nivolumab + ipilimumab in small cell lung cancer

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Background: Small cell lung cancer (SCLC) is an unmet medical need, representing ~15% of lung cancer diagnosed/year. Two-thirds of patients (pts) are diagnosed with extensive stage (ES) SCLC with a 2-year survival rate of 5%. Delta-like protein 3 (DLL3), an atypical Notch receptor family ligand, is highly expressed in SCLC and other neuroendocrine tumors with little to no expression in normal tissue. Rovalpituzumab tesirine (Rova-T,™) is an antibody-drug conjugate composed of a humanized DLL3-specific IgG1 monoclonal antibody tethered to a toxic DNA cross-linking agent. A Phase 1 study of Rova-T in SCLC pts showed encouraging progression-free survival and manageable safety profile. Studies show that nivolumab (nivo, anti-PD-1 antibody) +/- ipilimumab (ipi, anti-CTLA-4 antibody) has antitumor activity and is well-tolerated in 2nd-line SCLC. Given the complementary mechanisms of action and non-overlapping toxicities, further study is warranted to evaluate if combination of Rova-T and nivo, or all 3 agents leads to more pts with long-term responses and prolonged survival.

Trial design: This Phase 1/2 study (NCT03026166) will enroll ~90 pts in 3 cohorts. Each cohort will receive Rova-T 0.3 mg/kg IV on Day 1 of the 1st and 3rd 3-week cycle in combination with: nivo 360 mg/kg IV q4w x 2 cycles (cohort 1) or nivo 1 mg/kg q4w +ipi 1 mg/kg (cohort 2) or mfg/kg (cohort 3) IV q4w x 4 cycles. Maintenance nivo will be administered in all cohorts at 480 mg IV q4w. The dose limiting toxicity (DLT) evaluation period is 12 weeks. Pt eligibility: ≥ 18 years; histologically or cytologically confirmed 2nd-line or later ES SCLC, confirmed DLL3-positive status based on immunohistochemistry of baseline tumor tissue (for DLT evaluable pts); ECOG 0-1; no auto-immune disease; no prior exposure to immuno-oncology or pyrrolobenzodiazepine-based drugs. Primary and secondary objectives: assess safety and efficacy of Rova-T in combination with nivo or nivo + ipi. Exploratory objectives: assess expression of DLL3 and PD-L1 and their relationship to clinical outcome, pharmacokinetics, incidence of neutralizing antibodies, and effects on pharmacodynamic biomarkers. L. Rudin et al., Lancet Oncol, 2016.

Clinical trial identification: NCT03026166

Legal entity responsible for the study: AbbVie Scentrx

Funding: AbbVie Scentrx

Pre-chemotherapy nutritional status and chemotherapy response: An observational study


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Background: Cancer patients undergoing chemotherapy suffer from nausea, vomiting, low blood counts and electrolyte disturbances that impose stress on the nutritional needs of cancer patients. Nutritional status has been shown to reflect not just the patient’s general condition but also to predict patient survival. In this study, we evaluate the predictive effects of pre-chemotherapy nutritional status in patients with solid malignancies on chemotherapy response and quality of life.

Methods: Two hundred adult patients with localized solid malignancies undergoing Neoadjuvant/adjuvant chemotherapy were analyzed for their nutritional status before the therapy. Nutritional status was assessed using Subjective Global Assessment (SGA), Nutritional risk index (NRI), Body mass Index (BMI), Platelet lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR), and Albumin-globulin ratio (AGR) prior to their chemotherapy treatment. Patients were also assessed for Hand grip strength. Quality of life using Functional assessment of Chronic Illness Therapy (FACTIT) and EUROQol C30 and radiological response using RECIST criteria following chemotherapy.

Results: Mean age of study population was 51.65 ± 10.5 years. Multivariate regression analysis was done on Chemotherapy outcomes such as Response criteria, FACTIT scores, Quality of life scores and hand grip strength using, SGA, NRI, NLR, BMI and Albumin/ Globulin ratio as predictors. SGA score emerged as a significant primary predictor for hand grip strength (β = −7.3, p < 0.001) followed by BMI (β = 1.3, p < 0.001) and NRI (β = −0.73, p < 0.001). SGA emerged as a significant primary predictor for FACTIT score (β = 16.1, p < 0.001) followed by NLR (β = −61.4, p = 0.008). SGA emerged as a significant primary predictor for physical activity (β = 1.73, p < 0.001) followed by BMI (β = −0.19). SGA emerged as a significant predictor of quality of life score (β = −3.13, p < 0.001). Multinomial logistic regression for a complete response to RECIST criteria showed lower NLR to be a significant predictor (β = 0.90, p = 0.04).

Conclusions: The results suggest that pre-chemotherapy nutritional status and NLR influence the quality of life, strength and chemotherapy response in patients with solid malignancies.

Legal entity responsible for the study: Raghavendra Rao M
Funding: HCG Foundation
Disclosure: All authors have declared no conflicts of interest.

Anticipative approach to improve safety: An innovative daily hospital organisation


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Background: The PROCHE [Programme for optimisation of the chemotherapy network] initiative is an innovative oncology-monitoring program designed to reduce patient waiting time and chemotherapy wastage, ultimately improving patient care. A nurse calls patients 48 hours before anticancer treatment at the daily hospital to anticipate chemotherapy preparation.

Methods: Primary objective was to evaluate the incidence of different symptoms reported by grade (NCI-CTC AE) from 0 to 4 prospectively collected from 2008 to 2016. Secondary objective compared the 2009-2016 patients to the control cohort (2008 period) quantified using Mantel-Haenszel 12x3 and exact p-values.

Results: From January 2009 to December 2016, 3021 patients were enrolled in the program, representing 36 801 questionnaires completed over the whole period. Main adverse events (AE) were collected and compared to the control cohorts (2008, n = 513).

Table: 1542PD

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>2008 (%)</th>
<th>2009-2016 (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>82.4</td>
<td>62.01</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pain</td>
<td>49.69</td>
<td>28.31</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>35.77</td>
<td>39.06</td>
<td>0.0784</td>
</tr>
<tr>
<td>Nausea</td>
<td>29.92</td>
<td>11.38</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8.03</td>
<td>2.26</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Infection</td>
<td>7.91</td>
<td>3.48</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>diarrheaa</td>
<td>13.56</td>
<td>7.88</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Constipation</td>
<td>34.42</td>
<td>19.28</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dry Skin</td>
<td>38.72</td>
<td>25.21</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hand Foot Syndrome</td>
<td>15.28</td>
<td>2.47</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mucositis</td>
<td>15.54</td>
<td>9.87</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

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Development of an online drug-drug interaction resource to support prescribing of oncology medications


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Background: Patients treated for cancer are at high risk of drug-drug interactions (DDI), which affects nearly 60% of patients on therapy. We developed a freely available DDI resource (www.cancer-druginteractions.org) to support anti-cancer drug prescribing, based on successful implementation for HIV (www.hiv-druginteractions.org) and hepatitis (www.hep-druginteractions.org) treatments.

Methods: A review of literature and registration documents was performed to evaluate the available evidence for potential DDIs of several oncology decision trees. Based on the FDA guideline on DDI studies were used to assess clinical relevance of DDIs. Comedications that are frequently used by cancer patients were selected. Interaction potential of DDIs was classified using a straightforward traffic light classification and quality of evidence was classified using the GRADE system. Advice on management of the interaction was included where appropriate. All records were reviewed by an expert panel of clinical pharmacists/pharmacologists.

Results: Thus far, twelve targeted oncolytics for the indications renal cell, hepatocellular, and ovarian carcinoma, gastrointestinal stromal tumors, neuroendocrine tumors and sarcoma have been reviewed. Potential DDIs between oncolytics and > 450 comedications have been classified (Table). Tyrosine kinase inhibitors (TKI) show potential interactions which require action of prescribers in more than 20% of reviewed drug combinations. Monoclonal antibodies (MoAb) show clinically relevant DDIs in only 0.7% of reviewed drug combinations.

Table: 1544PD Overview of evaluated DDIs

<table>
<thead>
<tr>
<th>Drug class</th>
<th>TKI</th>
<th>MoAb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of comedications screened for interaction potential (mean)</td>
<td>458</td>
<td>478</td>
</tr>
<tr>
<td>Interaction class ('traffic light') (%)</td>
<td>64.8</td>
<td>80.6</td>
</tr>
<tr>
<td>Grade (A): clinically significant interaction</td>
<td>14.4</td>
<td>18.7</td>
</tr>
<tr>
<td>Intensity: no prior dosage adjustment required</td>
<td>17.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Amber: Potential interaction which may require dosage adjustment or close monitoring</td>
<td>3.3</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Conclusions: The DDI checker currently includes comprehensive and ready-to-use advice for DDIs with oncolytics for six indications (these are due to be expanded in the coming months). The freely available, independently developed website with 'traffic light' classification will facilitate health care professionals and patients’ awareness of potential DDIs between oncolytics and frequently used comedications.

Legal entity responsible for the study: Radboud University Medical Center
Funding: Abbvie, Astellas, AstraZeneca, Boehringer Ingelheim, Gilead, Pfizer

Disclosure: K. McAllister, S.H. Khoo: Educational grant from Abbvie and Gilead to perform this project. N.P. Van Erp: Educational grant from Astellas, AstraZeneca, Boehringer Ingelheim, Gilead and Pfizer to perform this project. All other authors have declared no conflicts of interest.
normal SM pts (RR: 1.89% CI: 0.82-2.90). Despite more frequent dose reductions at start, saracopenic pts did not have a significantly lower risk of DLT during CAPOX-B Tx (RR saracopenic vs normal SM pts: 0.86 95% CI: 0.46-1.45).

Conclusions: Saracopenia was significantly associated with dose reductions at start of CAPOX-B reinduction Tx, and not with DLT during CAPOX-B reinduction Tx. Possible explanations for dose reductions at start might be more frequent toxicities during previous Tx including neuropathy.

Clinical trial identification: NCT02517021
Legal entity responsible for the study: Helsinn Healthcare SA
Funding: Helsinn Healthcare SA
Disclosure: L. Schwartzberg: Served as a consultant for Helsinn, Tesaro, Eisai, and Merck and have received research funding from Helsinn and Tesaro. D. Vosin, G. Rizzi: Employee of Helsinn Healthcare. M. Karthaus: Served as and received honoraria for being a consultant for Helsinn and Riemter. All other authors have declared no conflicts of interest.

Table: 1548PD

<table>
<thead>
<tr>
<th>% Patients</th>
<th>NEPA (N = 412)</th>
<th>APR/GRAN (N = 416)</th>
<th>Risk Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIDL (overall domain)</td>
<td>Acute (0-24h) Delayed (25-120h)</td>
<td>86.2% 76.0%</td>
<td>83.2% 70.7%</td>
</tr>
<tr>
<td>NIDL (nausea domain)</td>
<td>Acute Delayed</td>
<td>81.8% 71.1%</td>
<td>80.0% 65.1%</td>
</tr>
<tr>
<td>NIDL (vomiting domain)</td>
<td>Acute Delayed</td>
<td>87.9% 83.1%</td>
<td>86.8% 77.4%</td>
</tr>
<tr>
<td>No Emesis</td>
<td>Acute Delayed</td>
<td>85.2% 79.4%</td>
<td>87.5% 76.2%</td>
</tr>
<tr>
<td>NSN</td>
<td>Acute Delayed</td>
<td>89.8% 78.2%</td>
<td>87.3% 72.8%</td>
</tr>
<tr>
<td>No RM</td>
<td>Acute Delayed</td>
<td>98.8% 97.6%</td>
<td>98.3% 94.7%</td>
</tr>
</tbody>
</table>

*statistically significant difference NEPA: fixed combination netupitant/palonosetron, APR: aprepitant, GRAN: granisetron, NIDL: no impact on daily life, NSN: no significant nausea, RM: rescue medication

Table: 1547PD

<table>
<thead>
<tr>
<th>Cycle 1 n (%) patients with</th>
<th>IV NEPA</th>
<th>Oral NEPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N = 203)</td>
<td>(N = 201)</td>
<td></td>
</tr>
<tr>
<td>At least one treatment emergent adverse event (TEAE)</td>
<td>120 (59.1%)</td>
<td>135 (67.2%)</td>
</tr>
<tr>
<td>Severe TEAEs</td>
<td>50 (24.6%)</td>
<td>51 (25.4%)</td>
</tr>
<tr>
<td>Serious TEAE</td>
<td>29 (14.3%)</td>
<td>21 (10.4%)</td>
</tr>
<tr>
<td>Any treatment-related TEAE (TRAE)</td>
<td>18 (8.9%)</td>
<td>19 (9.5%)</td>
</tr>
<tr>
<td>Most common (&gt;2%) TRAE Constipation</td>
<td>10 (4.9%)</td>
<td>11 (5.5%)</td>
</tr>
<tr>
<td>Serious TRAE</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any TRAE leading to discontinuation</td>
<td>1 (0.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Any TRAE resulting in death</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Conclusions: Intravenous NEPA was shown to be safe and well-tolerated with a similar safety profile to oral NEPA in patients with various solid tumors receiving HEC. Clinical trial identification: NCT00442631
Legal entity responsible for the study: Helsinn Healthcare, SA
Disclosure: L. Schwartzberg: Served as a consultant for Helsinn, Tesaro, Eisai, and Merck and have received research funding from Helsinn and Tesaro. D. Vosin, G. Rizzi: Employee of Helsinn Healthcare. M. Karthaus: Served as and received honoraria for being a consultant for Helsinn and Riemter. All other authors have declared no conflicts of interest.
rates during the overall (0-12 h) phase post-CT. All pts received dexamethasone on days 1-4. Secondary endpoints included proportion of pts with no emesis, no significant nausea (NSN: ≤25mm on 100mm VAS), no RM, and no impact on daily (NIDL) as assessed by the Functional Living Index—Emesis (FLIE), comprised of vomiting and nausea-specific questions/domains. The Cochran-Mantel-Haenszel test was used for between group comparisons; non-inferiority testing was not done for secondary endpoints. Results: Test groups were similar for the 828 pts analyzed: male (71%); mean age 55 years; lung cancer (58%); NIDL rates were higher for NEPA, particularly during the delayed phase; similar results were seen for no emesis, NSN, and no RM. Conclusions: In this first study comparing NK,RA regimes, NEPA administered only on day 1 was numerically similar to a 3-day oral APR/GRAN regimen in maintaining functional status in patients receiving highly emetogenic CT.

Legal entity responsible for the study: Helmin Healthcare, SA

Funding: Helmin Healthcare


1549P

Multicenter randomized controlled trial to evaluate the efficacy of frozen gloves for the prevention of chemotherapy-induced peripheral neuropathy

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Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of oxaliplatin and taxanes with a negative impact on quality of life (QOL). This study investigates the efficacy of wearing frozen gloves (FGs) during chemotherapy for the prevention of CIPN due to oxaliplatin or taxanes and the influence on patients’ QOL.

Methods: Patients with newly diagnosed cancer starting treatment with oxaliplatin, docetaxel or paclitaxel were eligible for this multicenter randomized controlled trial. Patients were randomized between wearing FGs on both hands during treatment or not wearing FGs. Self-reported CIPN and QOL were measured with the validated EORTC-QLQ C20 and EORTC-QLQ C30 at four time points: baseline (T0), after three cycles (T1), end of chemotherapy (T2) and after 6 months (T3). Subscales were analyzed with analysis of covariance and neuropathy symptoms with logistic regression analysis.

Results: Between February 2013 and May 2016, 181 patients were included, 90 patients in both arms. Thirty-one patients (34%) discontinued the FGs before end of chemotherapy mainly due to discomfort. Intention to treat analyses showed that patients in the FG-group experienced less tingling in fingers/hands at T1 (11% vs. 24%; p = 0.009) and T2 (28% vs. 43%; p = 0.038) compared to controls. At T3 these differences disappeared (28% vs 24%, p = 0.68). FG patients also experienced a trend towards less interference in handling small objects (2% vs 10%, p = 0.06) and opening a bottle (9% vs. 6%, p = 0.06) at T1. FG patients also reported significantly lower motoric problems (mean 8.3 (SD 9.7) vs. 12.8 (SD 13.6), p = 0.013) compared to controls at T3. Those treated with FGs reported statistically significant better QOL on EORTC-QLQ-C30 subscales physical (mean 82 vs. 74), role (mean 66 vs. 51), cognitive (mean 85 vs 78), and social functioning (mean 79 vs 67), and symptom scales fatigue (mean 40 vs 49) and appetite loss (mean 21 vs 34), all p < 0.05.

Conclusions: No long-term differences in neuropathy were found, but FGs reduced neuropathy symptoms with better QOL during chemotherapy. Future studies should focus on the biological process of cooling to prevent CIPN.

Clinical trial identification: NL39560.015.12

Legal entity responsible for the study: G. Vreugdenhil

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1551P

Risk factors of chemotherapy-induced nausea and vomiting during cisplatin regimens in antiemetic triplet regimens including palonosetron or granisetron: TRIPLE study (phase III)

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Background: Current antiemetic guidelines recommend antiemetic triplet regimens for cisplatin-based chemotherapy. Although several prior studies have identified risk factors for chemotherapy-induced nausea and vomiting (CINV), only a few have evaluated antiemetic triplet regimen, particularly with palonosetron. Therefore, the purpose of the present study was to confirm and compare the risk factors for CINV when using palonosetron or granisetron.

Methods: A total of 825 patients in the phase III clinical trial on cisplatin regimen were evaluated. The primary endpoint was complete response (CR) rate in the overall period (0-120 h). All patients were evaluated for CINV risk factors. Using a post-hoc analysis, the impact of antiemetic treatment on CR was assessed, and odds ratio (OR) with 95% confidence intervals (CIs) for antiemetic treatment failure were evaluated by using multivariate logistic regression models. CINV risk factors were also evaluated separately in each treatment group.

Results: The multivariate analysis revealed that female (OR: 2.572; 95% CI: 1.855–3.66), less than 60 years old (OR: 1.717; 95% CI: 1.252–2.35), the cisplatin dosage (OR: 1.017; 95% CI: 1.001–1.033), and granisetron use (OR: 1.357; 95% CI: 1.013–1.817) were all significantly associated with antiemetic treatment failure in the entire
Early Drug Development, Gustave Roussy Institute of Oncology, Villejuif, France,

Conclusions: This analysis revealed risk factors of CINV when using triplet antiemetic regimen Including palonosetron or granisetron for cisplatin. Palonosetron might be preferred for patients with one or more risk factors.

Clinical trial identification: Clinical trial information: UMIN 00004863 *UMIN: University Medical Information Network

Legal entity responsible for the study: Pharma Valley Center, Shizuoka Organization for Creation of Industries

Funding: Pharma Valley Center, Shizuoka Organization for Creation of Industries

Disclosure: T. Yamanaka: Research Funding; Taibo. K. Goto: Taibo, Chugai, Oto. N. Yamamoto: Consulting or Advisory Role; Chugai Pharmaceutical Co, Ltd, Omo Pharmaceutical Co. Ltd, Research Funding; Omo Pharmaceutical Co. Ltd, Taibo Pharmaceutical Co., Ltd. All other authors have declared no conflicts of interest.

Table: 1552P Antiemetic Utilization - European Oncology Nurse Survey

<table>
<thead>
<tr>
<th>Setting</th>
<th>Antiemetic Class</th>
<th>Antiemetics Utilized n (% respondents)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEC</td>
<td>5-HT3 RA NK, RA NEPA Steroid (eg, DEX)</td>
<td>Acute Phase (0-24h) 171 (81%) 130 (61%) 48 (23%) 173 (82%) 1 (0%) 35 (17%) 10 (5%) 63 (30%)</td>
</tr>
<tr>
<td></td>
<td>Phenothiazine Benzo diazepine Antipsychotic Metoclopamide</td>
<td>Delayed Phase (25-120h) 105 (50%) 92 (43%) 23 (11%) 133 (63%) 12 (6%) 25 (12%) 19 (9%) 103 (49%)</td>
</tr>
<tr>
<td>MEC</td>
<td>5-HT3 RA NK, RA NEPA Steroid (eg, DEX)</td>
<td>Acute Phase (0-24h) 183 (86%) 44 (21%) 17 (8%) 164 (77%) 3 (1%) 14 (7%) 5 (2%) 67 (32%)</td>
</tr>
<tr>
<td></td>
<td>Phenothiazine Antipsychotic Metoclopamide</td>
<td>Delayed Phase (25-120h) 100 (47%) 38 (18%) 19 (9%) 122 (58%) 10 (5%) 15 (7%) 13 (6%) 108 (51%)</td>
</tr>
</tbody>
</table>

HEC: highly emetogenic, MEC: moderately emetogenic, DEX: dexamethasone, NEPA: fixed combination of netupitant/palonosetron

Funding: Helsinn Healthcare, SA

Disclosure: P. Dietelenseger: Member of advisory boards of Helimun, Bayer Healthcare, Pfizer, Shire, Tesaro, Janssen, and BMS A. Young: Received honorarium from MSD (advisory board and presentations given), Helimun (advisory boards) and Chugai (presentation given). P. Jahn: Sponsor includes travel support; Helimun (2014). Current consulting or advisory role: Bristol-Myers Squibb, Chugai, Norgine, and CliniGen; Clinical Research Fund by Chugai. All other authors have declared no conflicts of interest.

1553P A pooled analysis evaluating the combination antiemetic therapy on chemotherapy-induced nausea and vomiting in patients with colorectal cancer receiving oxaliplatin-based chemotherapy of moderate emet risk


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Background: The incidence and risk factor of delayed chemotherapy-induced nausea and vomiting (CINV) for colorectal cancer (CRC) patients receiving oxaliplatin-based chemotherapy has not been clearly controlled. To evaluate the efficacy and risk factor of combination antiemetic treatment for delayed CINV in CRC patients receiving oxaliplatin-based chemotherapy.

Methods: Aggregated data were pooled from the two prospective observational studies and one clinical trial, A nationwide survey of CINV study group, the other prospective observational study in Japan and SENRI Trial in Japan. We assessed whether delayed CINV were controlled with 3 antiemetic treatment. We also evaluated risk factors by logistic regression analysis.

Results: A total of 661 patients were evaluable in this study. The median age was 64 (range: 19-85) with 381 males and 270 females. Three antiemetics were used in 220 (33.3%) patients. Delayed CINV were experienced more commonly in women than in men. Delayed nausea was well controlled with 3 antiemetics than with 2 antiemetics for women (38.3% vs. 52.8%; P=0.0295). Delayed vomiting was well controlled with 3 antiemetics than with 2 antiemetics for overall (4.1% vs. 15.9%; P=0.0001) and for women (5.3% vs. 24.4%; P=0.0001). We identified several risk factors; women (odds ratio [OR], 1.83; 95% confidence interval [CI], 1.26 to 2.59; P=0.0003), motion sickness (OR, 1.947; 95%CI, 1.230 to 2.832; P=0.004) and age (OR, 0.976; 95%CI, 0.961 to 0.991; P=0.0020) for delayed nausea, and women (OR, 2.447; 95%CI, 1.475 to 4.039; P=0.0005), motion sickness (OR, 1.892; 95%CI, 1.024 to 3.494; P=0.0417), 2 antiemetics (OR, 4.899; 95%CI, 2.362 to 10.122; P=0.0001), SNP (OR, 1.680; 95%CI, 1.028 to 2.747; P=0.0384) for delayed vomiting.

Conclusions: Three antiemetics combination are encouraged for CRC female patients treated with oxaliplatin-based chemotherapy to alleviate delayed CINV. Identification of individual risk factors will assist in the development of personalized treatments for delayed CINV.

Legal entity responsible for the study: N/A

Disclosure: All authors have declared no conflicts of interest.
Efficacy of neurokinin-1 receptor antagonists in the prevention of chemotherapy-induced nausea and vomiting in patients receiving carboplatin-based chemotherapy: a systematic review and meta-analysis

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Background: According to current ESMO – MASCC guidelines, a combination of a neurokinin-1 receptor antagonist (NK1RA), dexamethasone and a 5-HT3 receptor antagonist (5-HT3RA) is recommended to prevent carboplatin-induced emesis, with moderate level of confidence and not unanimous consensus. Our aim was to perform a meta-analysis of all randomized trials (RCTs) evaluating the role of NK1RA in the prevention of emesis for patients receiving carboplatin.

Methods: A systematic review was performed in January 2017, including RCTs comparing NK1RA + dexamethasone + 5-HT3RA vs. dexamethasone + 5-HT3RA in patients receiving first cycle of carboplatin-based chemotherapy. Primary outcome was complete response (CR), defined as no emesis and no use of rescue medication. CR was measured in W1 (acute phase), days 2-5 (delayed phase) and days 1-5 (overall period). A random effects model was applied.

Results: 9 trials were potentially eligible (7 aprepitant, 1 fosaprepitant, 1 rolapitant): 6 were RCTs including only patients receiving carboplatin, and 3 were subgroup analyses of patients receiving carboplatin within RCTs including various moderately emetogenic regimens. Data from 16 trials were potentially eligible (7 aprepitant, 6 fosaprepitant, 3 rolapitant) for comparison of response rates. The main results are reported below (CR at W1). There was no heterogeneity among trials. ID incidence remains constant between W6, 17 (15.2%) and W12 10 (11.6%). Localization was not correlated with FID or FID anaemia. Also, ID incidence remains constant between W6, 17 (15.2%) and W12 10 (11.6%). Localization was not correlated with FID or FID anaemia. Also, ID incidence remains constant between W6, 17 (15.2%) and W12 10 (11.6%). Localization was not correlated with FID or FID anaemia.

Conclusions: In patients receiving carboplatin-based chemotherapy, triple antiemetic therapy with NK1RA, dexamethasone and 5-HT3RA is associated with a statistically significant and clinically relevant improvement in CR, compared to 5-HT3RA plus dexamethasone. Individual patient data meta-analysis could help to identify patients who are likely to obtain the highest improvement from the addition of NK1RA.

Legal entity responsible for the study: Massimo Di Maio

Funding: None

Disclosure: M. Di Maio: Roles as advisor, and speaker’s fee for Merck Sharp & Dohme, Eli-Lilly, Bristol-Myers Squibb, and Novartis. All other authors have declared no conflicts of interest.

Pharmacokinetic (PK) study of a single oral dose of NEPA in Chinese healthy volunteers (HV’s)

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Background: NEPA, a combined neurokinin-1 receptor antagonist (RA) nутipitant (NETU, 300 mg) and 5-HT3RA-RA palonosetron (PALO, 50 mg), is the first approved oral combination antiemetic. NEPA has shown superior efficacy over PALO in preventing chemotherapy-induced nausea and vomiting (CNV), in placebo and AC chemotherapy settings, leading to its approval in the US and Europe (with 85% of patients Caucasian in the clinical trials). A recent phase 3 registration trial in Asian patients demonstrated non-inferiority of a single oral dose of NEPA in preventing CNV compared with a 3-day oral aprepitant/panciclon regimen. The present study was undertaken to assess the PK profile of NETU and PALO in Chinese HVs.

Methods: Eligible HVs received a single oral dose of NEPA administered as a hard gelatin capsule on day 1, after 10 h fasting. Blood samples for PK analysis were collected pre- and post-dose and at 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, and 240 h post-dose. The plasma concentration of NETU and PALO was determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS). PK parameters were estimated via non-compartmental analysis using the WinNonlin® software (Certara Inc., Princeton, NJ, USA).

Results: A total of 18 subjects were enrolled (16 male; mean body weight 62.7 kg [52.6–75.2 kg]; median age 27 y [21–37 y]). After a single oral dose of NEPA, mean (±SD) values of peak plasma concentration (Cmax) for NETU were 698 ± 217 ng/ml at a median of 4.5 h (Tmax 3–6 h), with mean (±SD) overall exposure up to the last measurable concentration (AUC0-t) of 20.2 ± 3.93 h×µg/ml. PALO plasma concentrations reached mean (±SD) Cmax of 1800 ± 252 ng/ml at 3 (2–6 h) with mean (±SD) AUC0-t of 57.6 ± 13.5 h×µg/L. NEPA was well tolerated in all HVs.

Conclusions: In Chinese HVs the PK profile of NEPA was comparable to that usually observed in Caucasians. For PALO, Cmax and AUC0-t were higher in these Chinese HVs compared to Caucasians, which may be explained by CYP2D6 (involved in the metabolism of PALO) polymorphism. However, the similar efficacy and safety for PALO and NEPA in pivotal studies in both populations suggests that the higher exposure to PALO in Chinese HVs is unlikely to be clinically relevant.

Legal entity responsible for the study: Helsinn Healthcare SA

Funding: Helsinn Healthcare SA

Disclosures: S. Chessari, C. Lanzarotti, A. Bernareggi: Helsinn Healthcare SA Employee All other authors have declared no conflicts of interest.

Table 1556P

<table>
<thead>
<tr>
<th>Location N (%)</th>
<th>Anaemia N (%)</th>
<th>Functional iron deficiency N (%)</th>
<th>Absolute iron deficiency N (%)</th>
<th>Functional ID associated with Anaemia N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location N (%)</td>
<td>W0</td>
<td>W6</td>
<td>W12</td>
<td>W0</td>
</tr>
<tr>
<td>Breast 36 (30)</td>
<td>13 (36.1)</td>
<td>20 (64.5)</td>
<td>17 (63.0)</td>
<td>15 (41.7)</td>
</tr>
<tr>
<td>Colorectal 27 (23)</td>
<td>20 (74.1)</td>
<td>16 (72.7)</td>
<td>11 (68.8)</td>
<td>14 (51.9)</td>
</tr>
<tr>
<td>Lung 26 (24)</td>
<td>16 (62.3)</td>
<td>22 (88.0)</td>
<td>14 (93.9)</td>
<td>13 (48.1)</td>
</tr>
<tr>
<td>Prostate 12 (10)</td>
<td>9 (75.0)</td>
<td>11 (91.7)</td>
<td>9 (81.8)</td>
<td>6 (55.6)</td>
</tr>
<tr>
<td>All solid tumours 119 (100)</td>
<td>63 (52.9)</td>
<td>75 (62.8)</td>
<td>56 (47.8)</td>
<td>62 (50.0)</td>
</tr>
</tbody>
</table>

At W0, 62 patients (48%) had FID, 32 (26.9%) had FID associated with anaemia and 9 (7%) had AID. FID prevalence remains constant from W0 to W12, so as FID anaemia and AID. Also, ID incidence remains constant between W6, 17 (15.2%) and W12 10 (11.6%). Localization was not correlated with FID or FID anaemia but prevalence of AID is higher for colorectal tumours. (evaluated at W12) was significantly correlated (p = 0.04) with tumour response at W12, 51.2% of responders among patients with no ID versus only 33.3% among patients with ID.
Conclusions: Our data confirm the high prevalence of ID in cancer patients. Localization is not correlated with the prevalence of ID whereas absolute ID is of higher rate in colorectal cancer. Also, ID at W12 without supplementation seems to be predictive of chemotherapy response.

Clinical trial identification: NCT01968004. Release date: October 1, 2013

Legal entity responsible for the study: Centre Antoine Lacassagne

Funding: Vifor Pharma France

Disclosure: All authors have declared no conflicts of interest.

### 1557P

Nutritional risk as a predictor of short-term outcomes in a prospective cohort of elderly patients with cancer

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Background: To determine if the nutritional risk identified by the Mini Nutritional Assessment Short-Form (MNA-SF) is an independent predictor of short-term outcomes (infection, hospitalization and premature death).

Methods: prospective cohort study of elderly patients (≥60 years) with a recent diagnosis of cancer admitted to an outpatient oncology unit was performed. Sociodemographic and clinical variables and MNA-SF were collected at baseline. The outcomes were healthcare-associated infection, hospitalization and death. Data were analysed using the multivariable Cox proportional hazards models. Overall survival was estimated using the Kaplan–Meier method and survival curves were compared using the Log rank test.

Results: he cohort consisted of 608 elderly patients followed for 180 days. The mean age was 71.9 years (range: 60–96) and 50.2% participants were at risk of malnutrition as measured by the MNA-SF. During follow-up, 35.3% of patients were hospitalised, 29.4% had healthcare-associated infections and 16.4% died. After adjustment for clinical variables and MNA-SF, higher risk of death (HR = 1.88, 95%CI 1.32–2.67, \( p = 0.012 \)) and death (HR = 3.12, 95% CI: 1.74–5.78, \( p = 0.001 \)) hospitalization (HR = 5.12, 95% CI: 1.74–5.78, \( p = 0.001 \)).

Conclusions: Nutritional risk at admission was identified as a significant predictor of risk for premature death, infection, and need for hospitalization in elderly cancer patients. The use of MNA-SF should be incorporated into regular geriatric assessment of older patients with cancer.

Legal entity responsible for the study: Jurema Telles De Oliveira Lima

Funding: FACEPE CNPQ

Disclosure: All authors have declared no conflicts of interest.

### 1558P

A patient-centered approach to the re-development of supportive care services for oncology adolescent and young adult (AYA) patients (pts) across McGill University hospitals (Rossy Cancer Network-RCN)

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Background: FOLFIRINOX is an active yet toxic regimen against intestinal cancers. Improving its tolerability could widen its use in routine clinical practice.

Circadian-based chronobiology of FOLFIRINOX has been described, however, its tolerability was not systematically assessed. Here, we report the results of a prospective cohort study designed to analyse the dynamic patterns of relevant parameters and to assess dose adjustment in real-time.

Methods: a) FOLFIRINOX was administered every 2 weeks at home. Pts received Day (D)1 chrono I (180 mg/m2, over 6-h; peak rate at 5:00), and chrono III (400 mg/m2/d, over 11.5-h; peak rate at 04:00), q2 weeks at home. Pts received Day (D)1 chrono I (180 mg/m2, over 6-h; peak rate at 5:00), and chrono III (400 mg/m2/d, over 11.5-h; peak rate at 04:00), q2 weeks at home.

Results: Pts completed the 19-item MD Anderson Symptom Inventory (MDASI) on an interactive electronic screen, weighed themselves on a dedicated scale, and continuously wore a watch-sized wrist-accelerometer for CircAct and sleep monitoring. Daily data were securely teletransmitted via Internet to a specific server accessible by the hospital team. The validated and clinically-relevant CircAct parameter (L) and sleep efficiency (SE) were calculated. The dynamic patterns over time of PROMs, BWC, I and oxaliplatin (O) chronoIFLO4 combination at home.

Conclusions: Future studies are needed to confirm the results and further assess the potential of FOLFIRINOX treatment home.

Legal entity responsible for the study: Pett Kavan

Funding: Rossy Cancer Network

Disclosure: All authors have declared no conflicts of interest.

### Table 1558P Sample Strategies for Improving Patient Quality of Life and Quality of Care Throughout the Cancer Care Continuum

<table>
<thead>
<tr>
<th>Patient Panel (n = 31)</th>
<th>Importance Score (0-7 Likert scale)</th>
<th>Health Care Professionals Panel (n = 31)</th>
<th>Importance Score (0-7 Likert scale)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient education programs that provide AYAs with knowledge regarding treatment options and the potential physical and QOL implications of cancer therapy</td>
<td>6.55</td>
<td>4</td>
<td>6.45</td>
</tr>
<tr>
<td>Inform reproductive-age patients of cancer-related fertility risks as early in the treatment planning as possible (as per ASCO guideline) and refer as needed to an appropriate fertility preservation specialist</td>
<td>6.42</td>
<td>2</td>
<td>6.58</td>
</tr>
<tr>
<td>Provide access to a systematic and standardized symptom management, pain control, and palliative care program</td>
<td>6.35</td>
<td>1</td>
<td>6.65</td>
</tr>
</tbody>
</table>
Results: Eleven patients (48–72 years; 45% males; 27% PS = 0) received 26 cycles (cy) of chemotherapy, and provided 5,891 data points/8,736 expected (67.4%). No grade 3-4 clinical toxicity occurred. The most severe MDASI scores remained low: interference with work (mean: 5.1/10) or general activity (4.9); fatigue (4.9); distress (4.2) and appetite loss (3.6). Mean BWC was 0.9%; and mean SE remained above 82%. CTCAE disruption (I<CO <59.5%) was observed in ≤ (15%) cys before chemotherapy start and in ≤ (19%) cys at D14.

Conclusions: ChronoFLO4 represents a safe therapeutic option at home, and the pre-centered multidimensional telemonitoring solution allows the design of innovative management approaches, ultimately improving pt experience with chemotherapy, safety and outcomes.

Legal entity responsible for the study: INSERM and European Commission

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1560P A pilot study to evaluate the feasibility, usability, and perceived satisfaction with eCO (Cediranib-Olaparib), a mobile application for side effect monitoring and reporting, in women with recurrent ovarian cancer


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Background: Cediranib inhibits VEGFR1–3 with significant but treatable side effects of hypertension and diarrhea. High frequency of these events occurred in a trial of cediranib with olaparib (C+O). Effective control of these side effects is therefore important for C+O therapy. eCO, a cloud-based mobile medical device, was developed to provide secure capture, storage, and transmission of accurate BP and diarrhea data to aid in remote monitoring. Pts receive automated reminders and instructions for self-management based on severity. HCPS monitor pt status via a secure web portal and email alerts.

Methods: Pts enrolled in a Ph 2 study of C+O (NCT02345265) could opt to participate in this pilot study. Pts received eCO-based prompts, used eCO to record BP via a Bluetooth-linked BP cuff and to enter diarrheal events, and received eCO-based reminders and recommendations. Pts completed a 17-item usability and satisfaction questionnaire after 4 weeks of eCO use. The primary objective was to evaluate the feasibility, usability, and satisfaction of eCO use. Data were analyzed by Wilcoxon Rank Sum Analysis.

Results: 15 pts completed the pilot study. Pts indicated they felt closely monitored, connected with the healthcare team, involved in their own care, and satisfied with ease of learning and use of many eCO functions (alpha < .01). Pts were satisfied with diarrhea entry and finding past recommendations (alpha < .05) and were not satisfied with reporting diarrheal side effects. eCO captured 98.1% of expected BP values (94.3% direct upload; 5.8% manual entry). BP events ≥2 consecutive BP >140/90 mmHg occurred in 11 pts (6 with 1 event, 2 with 2 events, 3 with 5 events) with median duration 5 days (range 3–28 days). 12 pts reported 20 diarrheal events (range 1–4 events); median duration was 1 day (range 1–2.7 days); 31 entries were made (28 Gr 1, 3 Gr 2).

Conclusions: In this initial pilot, eCO captured accurate BP and diarrhea events from pts for remote monitoring. Pts reported overall usability and satisfaction with eCO, especially feeling closely monitored, more connected, involved in self-care and ease-of-use. Use of eCO in other studies is planned.

Clinical trial identification: NCT02345265

Legal entity responsible for the study: National Cancer Institute

Funding: National Cancer Institute


1561P Study of the satisfaction level of an education program for cancer patients


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Background: As the demand for cancer patient education has increased lately, the administrative body of the universal health insurance in South Korea has decided to include the cost for cancer patient education to its insurance coverage. Dongnam Institute of Radiological Medical Sciences (DIRAMS) in Busan, South Korea, created its cancer patient education program in 2016 and has educated cancer patients about their treatments according to the program since then. This paper will discuss the study conducted at the hospital in order to estimate the level of satisfaction among the patients who participated in the education program.

Methods: The program consists of an 80-min long education session led by a doctor, a nurse, and a clinical dietitian before each cancer patient receives his or her chemotherapy, radiation therapy, or a surgery. Questionnaire survey was conducted on patients who participated in the education program from July 2016 to March 2017.

Results: Among the patients who participated in the survey, the number of patients who had chemotherapy education was 663. Stomach cancer was the most prevalent cancer type in this group, followed by cholangiocarcinoma. 75.3% of the patients in this group received palliative chemotherapy, and the rest received adjuvant chemotherapy. The satisfaction level of the chemotherapy education was 4.98 on a five-point Likert scale. The number of patients who had the radiotherapy education was 193. Breast cancer represents the largest portion in this group. The satisfaction level of the radiotherapy education was 4.3. The number of patients who received the surgery education was 70. The satisfaction level of the surgery education was 4.6.

Conclusions: The total 928 patients who participated in the education program rate their level of satisfaction as 4.8 on average on a scale of 1 to 5. This high rating can be seen as an indication of high satisfaction in the quality of the education about their treatments. To enhance the education program further, it will be worthwhile to investigate improvements in each part of the program and in the perspective of patients. Subsequently, it is also worthwhile to investigate how the education program affects cancer patients.

Legal entity responsible for the study: Ha Young Lee

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1562P Factors influencing the use of thromboprophylaxis in cancer outpatients: CAT AXIS, a case-vignette study on clinical practice

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Background: Data on long-term venous thromboembolism (VTE) prophylaxis in cancer outpatients remain scarce. In the absence of consistent treatment guidelines, our objective was to describe clinical practice and to identify factors influencing the use of thromboprophylaxis.

Methods: CAT AXIS was a multicenter cross-sectional study based on the completion of physician-profile questionnaires and the assessment of 10 e-mailed credible clinical scenarios of lung, colon and breast cancer as each of participants using the case-vignettes validated method.

Results: A total of 224 physicians participated allowing the completion and the analysis of 2,085 case vignettes corresponding to 765, 703 and 617 fictive clinical scenarios on lung, colon and breast cancers, respectively. The overall rate of thromboprophylaxis was 681/2085 (32.6%) among participants with a comparable proportion for the three types of cancer. Low-molecular-weight heparin (LMWH) was the most frequently used, by 92.7%, 93.8% (32.6%) among participants with a comparable proportion for the three types of cancer. "Low-molecular-weight heparin (LMWH)" was the most frequently used, by 92.7%, 93.8% (32.6%) among participants with a comparable proportion for the three types of cancer. Other types of prophylaxis used were direct oral anticoagulants (DOAC) and fondaparinux, with rates ranging from 7.3% to 7.9%.

Conclusion: In conclusion, this study has shown a global low rate of thromboprophylaxis in cancer outpatients, with a similar level of use across the three types of cancer. The main obstacle cited was the absence of evidence to support the use of prophylaxis. However, the majority of participants would consider using prophylaxis in eligible patients, highlighting the need for further research in this field.

Legal entity responsible for the study: Ha Young Lee

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Supportive care
Table: 1562P Factors influencing the prescription of thromboprophylaxis

<table>
<thead>
<tr>
<th></th>
<th>Lung cancer</th>
<th>Colon cancer</th>
<th>Breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR [95% CI]</td>
<td>p</td>
<td>OR [95% CI]</td>
</tr>
<tr>
<td>ECOG index score: 3 vs 0-2</td>
<td>3.3 [2.4; 4.6]</td>
<td>&lt;0.01</td>
<td>2.4 [1.7; 3.6]</td>
</tr>
<tr>
<td>Antineoplastic treatment: Chemotherapy+targeted therapy (TT) vs TT only</td>
<td>2.1 [1.3; 3.6]</td>
<td>2.8 [1.5; 5.2]</td>
<td>2.2 [1.2; 3.9]</td>
</tr>
<tr>
<td>History of VTE: Yes vs no</td>
<td>1.9 [1.3; 2.5]</td>
<td>&lt;0.01</td>
<td>1.7 [1.2; 2.4]</td>
</tr>
<tr>
<td>Cancer stage: Metastatic vs local</td>
<td>1.6 [0.9; 2.7]</td>
<td>0.088</td>
<td>N/A</td>
</tr>
</tbody>
</table>

NI: not included in the analysis.

Table: 1563P Study Design and Endpoints TPOR Agonist vs. Control (Range study incidences)

<table>
<thead>
<tr>
<th>Safety Endpoint</th>
<th>Lung cancer</th>
<th>Colon cancer</th>
<th>Breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3-4 thrombocytopenia</td>
<td>Grade 3: 54%</td>
<td>Grade 4: 14%</td>
<td>Grade 3: 85%</td>
</tr>
<tr>
<td>Platelet transfusions</td>
<td>11%</td>
<td>30%</td>
<td>N/A</td>
</tr>
<tr>
<td>Safety Endpoint</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Bleeding</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Conclusions: While TPOR agonists have not been approved for use in CIT, this literature review suggests that TPOR agonists may increase platelet counts and decrease chemotherapy dose delay/reduction. Further study with well-characterized bleeding and platelet thresholds is needed to explore the possible benefits of TPOR agonists for CIT compared with current care options (eg, transfusions, dose reduction).

Legal entity responsible for the study: Amgen Inc.
Random optimization interactive system based on Kernel learning (RISK) for venous thromboembolism risk assessment in chemotherapy-treated cancer patients

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Background: Using a combined approach of Kernel machine-learning (ML) and random optimization (RO) techniques we recently developed a set of predictors (ML-ROs) for VTE risk assessment. Aim of this study was to validate a model incorporating the two best ML-ROs to devise a web-based graphical interface for VTE risk stratification.

Methods: Pre-chemotherapy age, sex, tumor site and stage, hematological attributes, fasting blood lipids, glyceric indexes, liver and kidney function, BMI, ECOG, support-ive and anti-cancer drugs of 608 cancer outpatients were entered in the model, with numerical attributes analyzed as continuous values. Variables were clustered into groups according to clinical significance, and RO was used to devise their relative weight in final prediction.

Results: VTE occurred in 7.1% of patients. Overall, 46% were at high-risk for VTE, as per current guidelines (Khorana Score (KS): >3), 11% of which had VTE during treatment. 42% and 32% were at intermediate (KS 1-2) or low-risk (KS = 0), with VTE rates of 9% and 5%, respectively. Accordingly, the performance of KS, despite a 94% specificity, was characterized by a 9% sensitivity with an area under the ROC curve (AUC) of 0.589, translating into non-significant positive (+LR) [1.58 (0.48-4.30)] or negative likelihood ratio (-LR) [0.96 (0.83-1.04)]. Conversely, the VTE risk prediction performance of the combined ML model showed a 0.716 AUC, which was significantly higher than that observed with KS (difference between areas: 0.127, p = 0.004). At a criterion >1 (risk estimate achieved by both predictors) this combined approach showed significant +LR [2.30 (1.70-2.82)] and -LR [0.46 (0.28-0.69)] and a 4.9 Hazard Ratio (95%CI: 2.5-9.4) with a 6-month VTE rate of 3.4% in the low-risk, compared with 14.9% in the high-risk category.

Conclusions: These results demonstrate that a ML approach, optimizing the relative weight (by RO) of groups of clinical attributes, is of clinical value for VTE risk prediction, performing better than KS. We are now finalizing the architecture of a web service with a graphical interface helping oncologists in the critical phase of decision making.

Legal entity responsible for the study: Risk Research Group

Funding: European Social Fund PON03PE_00146_1/10 BIBIOFAR

Disclosure: All authors have declared no conflicts of interest.

Association between systemic inflammation and symptoms in advanced cancer patients

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Background: There is growing evidence relating inflammation as a prognostic factor in cancer patients. Previous reports have found a small but significant association between systemic inflammation and symptoms in advanced cancer patients. The aim of this study was to analyse the relationship between systemic inflammatory response markers with the symptoms and performance status of advanced cancer patients that have been admitted to an Acute Palliative Care Unit (PCU).

Methods: We conducted an observational study including all cancer patients admitted in the PCU between January 2012 and April 2015. We performed a correlation analysis (spœrnian’s rho) between serum C-reactive-protein (CRP), the modified Glasgow Prognostic Score (mGPS) and Neutrophil-to Lymphocyte Ratio (NLR) with patients symptoms recorded as the Edmonton Symptom Assessment System (ESAS) and performance status recorded as Eastern Cooperative Oncology Group (ECOG), Barthel Index and Palliative Performance Scale (PPS). All data were collected within the first two days of admission.

Results: Data of 951 patients were available. The median survival was 17 days. CRP was significantly correlated with ECOG (p=0.180, P=0.000), dyspnoea (p=0.079, P=0.019), fatigue (p=0.162, P<0.001), anorexia (p=0.103, P=0.002), somnolence (p=0.096, P=0.009), wellbeing (p=0.012, P<0.001), Barthel (p=0.178, P<0.001) and PPS (p=0.173, P<0.001). In relation to mGPS, a significant correlation was found with ECOG (0.116, P=0.001), fatigue (p=0.184, P<0.001), anorexia (p=0.107, P=0.003), somnolence (p=0.080, P=0.037), Barthel (p=0.127, P<0.001) and PPS (p=0.125, P<0.001). Finally, NLR was significantly correlated with ECOG (p=0.112, P<0.001), dyspnoea (p=0.117, P<0.001), fatigue (p=0.107, P=0.002), Barthel (p=0.115, P<0.001) and PPS (p=0.100, P=0.002).

Conclusions: There is a small but significant correlation between systemic inflammation and symptoms. Further studies are needed to confirm the results and to test this relation in earlier phases of the disease.

Legal entity responsible for the study: Hospital Universitario La Paz

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Outcomes of patients with malignancy admitted to the intensive care units (ICU): A prospective study

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Background: Decisions regarding whether advanced cancer patients should be admitted to the intensive care units (ICU) is based on a complex suite of considerations, including short and long term prognosis, quality of life, and options to treat cancer. We set to describe demographic, clinical, and survival data and to identify factors associated with short and long term mortality in critically ill advanced cancer patients with non-elective admissions to general ICUs.

Methods: Critically ill adult cancer patients non-electively admitted to the ICUs at the American University of Beirut Medical Center (AUBMC) between August 2015 and 2016 were included. Demographic, clinical, and laboratory data was prospectively collected from first day of ICU admission up to 30 days after discharge. This study was observational and clinical decisions were left to the ICU team and attending physician.

Results: 91 patients were enrolled between August 2015 and 2016, with 41 patients (46%) dying in the ICU, and 12 patients (13.5%) within 30-days post-discharge. 7 patients were lost to follow-up. Mean OS was 137 days, and median OS was 31 days since date of admission to the ICU. Most common reasons for ICU admission were sepsis (68.5%) and respiratory failure (19%). Cox regression showed direct admission from the ED (2.4 times more likely to die), those with uncontrolled malignancies (1.8 times), chemotherapy within the last 30 days prior to ICU admission (2.3 times), and development of multi-organ failure (MOF) (2.5 times) in the ICU are major predictors of poor prognosis.

Conclusions: Our study showed receiving chemotherapy within thirty days prior to admission as a predictor of poor outcome in univariate and multivariate analyses. This has not been reported in a study population of this kind before. Also, many studies state that developing MOF, whether in the ICU or prior to admission negative prognostic factor. Finally, our study found that direct admission from the ED is a negative prognostic factor, which has only been reported for hematological malignancies in other studies. Thus, there is a need for the development of proper admission criteria for this population.

Legal entity responsible for the study: American University of Beirut Medical Center

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Management of thrombosis in cancer patients in Greece

Hellenic Society of Medical Oncology (HeSMO), Athens, Greece

Background: Venous thromboembolism (VTE) is a common cause of adverse outcomes in patients with cancer. The risk of VTE varies with cancer type, stage, grade, therapy and other patient characteristics. Low-molecular-weight heparin (LMWH) remains the standard therapy for VTE in cancer patients.

Methods: This is an observational study conducted by the Hellenic Society of Medical Oncologists (HeSMO) that aims to record and highlight the current clinical practice and management of VTE in patients with cancer in 18 Greek centers, with nationwide dispersion.

Results: The participating centers reported a total of approximately 4380 cancer patients managed on a monthly basis, where the vast majority (90%) were treated in an outpatient setting. For this study, 340 patients with active cancer were enrolled, with the following characteristics: 53.2% male; mean age 64.3; 62.1% of patients had PS of 0-1; tumor types: lung 22.3%, pancreas 16.3%, colon 13.6%, breast 11%, stomach 8.3%, ovarian 6.5% and other tumors 21.7%. The majority of patients (95.3%) received anticancer therapy; 21.3% were inpatients and 78.6% outpatients. Among these 340 patients, 86 were diagnosed with VTE; 81.4% had symptomatic VTE while 16.6% had incidental VTE. Regarding patients with VTE, 94.2% received anticoagulation therapy and the majority of these (65.1%) were treated in an outpatient setting. Of the patients diagnosed with VTE, 76.9% had performance status 0-1 and 74.4% had metastatic disease. In the metastatic stage there was differences in the incidence of symptomatic or incidental VTE, 75% vs 74.3% respectively (p = 0.99). Highest percentage of incidental VTE observed was in patients with lung cancer (43.8%), followed by pancreatic (18.8%) and colon cancer (12.5%). All patients with VTE received antithrombotic treatment with LMWH according to the current clinical guidelines.

Conclusions: The majority of patients who developed VTE were inpatients undergoing anticancer treatment with metastases. Incidental VTE was more frequent in patients with lung cancer. Our findings of 16.8% incidental VTE further confirm the previously published results in similar studies.

Legal entity responsible for the study: Hellenic Society of Medical Oncology (HeSMO)

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Incidence and outcome of Incidental Pulmonary Embolism (IPE) in oncology patients with current macroscopic disease

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Background: IPE is defined as a PE detected on a CT scan (not a pulmonary angiogram) done for reasons other than suspected PE. This study is to evaluate the incidence of IPE in oncology patients with current macroscopic disease, and the outcome that remains the standard therapy for VTE in cancer patients.

Methods: Patients with lung cancer. Our findings of 18.6% incidental VTE further confirm the previously published results in similar studies.

Results: 2147 scans were identified. 543 scans were excluded due to absence of macroscopic disease (No IPE was reported in any of these scans.) leaving 1604 scans eligible for this study. Incidence for different tumour types is shown in the table 1. 26 IPE patients are female = 15; median age = 66 (range 22 – 90); main artery = 9, lobar artery = 5; average age from CT scan to anticoagulation (LMWH) therapy is 9.7 days (median = 5; days; range 0 – 61 days; no treatment in 3 patients) mainly due to the delay in reporting (median = 1 day; range 0 – 60 days). The median survival from the scan date is 7 months (range 1 – 22) with 9 patients still alive and 2 lost to follow up. None of the patients whose anticoagulation started 5 or more days after the CT scan died within 3 months. IPE was absent in all subsequent CT scans. This happened without any anticoagulation therapy in one patient who had a segmental IPE. Table 1. Incidence of IPE for different tumour types

<table>
<thead>
<tr>
<th>Table:1569P</th>
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<tbody>
<tr>
<td>Patients</td>
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<tr>
<td>------------</td>
</tr>
<tr>
<td>Lung</td>
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<tr>
<td>Breast</td>
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<td>Colorectal</td>
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<td>Oeso/gastric</td>
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<td>CUP</td>
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<td>Bladder</td>
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<tr>
<td>Pancreas</td>
</tr>
<tr>
<td>Skin</td>
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<td>Total</td>
</tr>
</tbody>
</table>

Table 1: Incidence and outcome of Incidental Pulmonary Embolism (IPE) in oncology patients with current macroscopic disease

Immune related adverse events associated with ipilimumab and nivolumab

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Background: Immune related adverse events (IrAEs) are unique and completely different from what we have seen previously. There is no prospective data on these toxicities and guidelines are based on symptomatic management from ongoing clinical trials. Ipilimumab and nivolumab induce irAEs to the skin, gastrointestinal, liver, endocrine and other systems.

Methods: A retrospective review of data from 45 patient records were used to describe the irAEs associated with 19 patients treated with Ipilimumab and 25 patients treated with Nivolumab and 1 patient with combination of ipilimumab and nivolumab. This is a single centre review in an expanded access programme/c clinical trial setting.

Results: A total of 45 patients (28 males, 17 females) were analyzed. The median age was 63 years. Three patients with metastatic melanoma, 18 with non-small cell lung cancer (NSCLC), 2 with renal cell carcinoma and 2 with Hodgkin’s disease were treated with nivolumab and 19 with metastatic melanoma received ipilimumab. One patient with combination of ipilimumab and nivolumab. In total 167 cycles of nivolumab (median = 4, range 1-16) and 60 cycles of ipilimumab (median = 4 cycles, range 1-4) were administered. The patient receiving combination of ipilimumab and nivolumab received 1 cycle. Seven IrAEs are described in 15 ipilimumab treated patients. These include endocrinopathy in 5 patients (hypophysitis in patient and hypothyroidism in 2 patients), colitis in 3 patients (1 required infliximab) and hepatitis in 1 patient. Among the patients treated with nivolumab, 7 IrAEs were documented. These included pneumonitis in 2 patients, skin rash in 3 patients, mild diarrhea in 1 patient and mild uveitis in 1 patient. One patient developed autoimmune thrombocytopenia, and nephritis. Three chest infections were documented including pulmonary tuberculosis in a NSCLC patient. The patient receiving combination ipilimumab and nivolumab had grade 4 skin toxicity requiring treatment discontinuation. No IrAE related deaths were documented.

Conclusions: A plethora of irAEs are described with anti-PD1 and anti-CTLA4 antibodies. Colitis was more common with ipilimumab while pneumonitis more common with nivolumab. Prompt IrAEs’s diagnosis will result in decreased morbidity and mortality.
Febrile Neutropenia: a systematic review of the first 5 years of a cancer unit


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Background: Febrile Neutropenia (FN) is a potentially life-threatening and dose-limiting complication of myelosuppressive chemotherapy (CT) that often requires hospital admission (HA). Patients (pts) with FN must initiate antibiotic (ab) therapy promptly and delay in diagnosis and subsequent treatment are associated with higher morbidity and mortality.

Methods: Retrospective single institution review of all FN episodes that occurred in the years 2012 to 2016 in pts with solid tumors with an absolute neutrophil count (ANC) < 1,000/μL and blood cultures (BC) collected within 30 days of an IV CT treatment. With a population base of 278,000 individuals, and 550 new solid tumor pts in Medical Oncology per year, we reviewed all BC, collected during the first 5 years of Hospital Beatriz Angelo (2012-2016) and crossed with the registry of pts treated with IV CT. FN was defined as a tympanic temperature > 38 °C and ANC < 1,000/μL and expected to decrease to < 500/μL in the following 7 days. Pts with hematologic malignancies were excluded.

Results: Among 1,947 eligible pts, 152 had a FN (8%) with a total of 173 FN episodes. Median age was 67 yo; 90 were males (59%). Median initial ANC was 310/μL in 69% and < 100/μL in 17%. In the emergency room, median time from hospital nurse triage to medical observation (MO) was 38 min (range 4min-6h11m), MO to blood count specimen withdrawal 55min (range 10min-6h43m) and MO to arrival of BC to the lab 5h1min (range 24min-250dmin). 33 FN episodes were associated with positive BC (19%, 6 with two agents), 11 BC with Gram positive and 28 with Gram negative bacteria. 157 episodes led to HA (90%), 15 were treated as outpatients and in 1 FN episode the pt died at presentation from E. coli pneumonia. Median days of hospitalization was 8 (range 0-36). Median time on ab was 9 days (range 1-35), with first line regimen including piperacillin/tazobactam in 110, amoxicillin/avulacillin and cephalosporin in 17, meropenem in 9, other agents in 11 in 1 and no treatment. Mortality during the FN episode was 20% (n = 34) from 173 FN episodes.

Conclusions: FN is a serious and common complication of CT treatment which must be diagnosed and treated rapidly. Delays in the evaluation of fever and FN episodes may compromise the outcome of these pts.

Legal entity responsible for the study: Ioão Moreira Pinto

Funding: None

Disclosure: All authors have declared no conflicts of interest.

G-CSF and G-CSF biosimilars: a meta-analysis of randomized clinical trials in breast cancer patients

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Background: The granulocyte colony-stimulating factors (G-CSFs) filgrastim and pegfilgrastim are widely used to prevent neutropenia in cancer patients undergoing myelosuppressive chemotherapy. Several G-CSF biosimilars are available, their development involving a step-wise approach including analytical comparison with the reference and iterative process development. Randomized clinical trials (RCTs) have confirmed that the biosimilar product and its biosimilar provide the same clinical efficacy and safety and play pivotal role in the totality of evidence concept. However some heterogeneity exists among the studies. For G-CSF biosimilars, patients with breast cancer (BC) are the most sensitive population in which to confirm similarity. The aim of this meta-analysis was to compare the clinical efficacy of approved or proposed G-CSF biosimilars (filgrastim or pegfilgrastim) with reference G-CSF in patients with BC.

Methods: A Medline literature search up to March 2017 identified randomized clinical trials (RCTs) comparing biosimilar G-CSF to reference G-CSF in BC patients. Primary efficacy endpoint was mean difference in duration of severe neutropenia (DSN). Secondary efficacy measures were differences in depth of absolute neutrophil count (ANC) nadir and time to ANC recovery. Random effect models were fitted to obtain pooled estimates of the mean difference and their corresponding 95% confidence intervals (CIs).

Results: Eight eligible RCTs were included. Overall difference in DSN between reference and biosimilar medicines was not statistically significant (0.06 days [95% CI -0.05, 0.17]) (Table). The secondary efficacy endpoints also showed no significant differences between reference and biosimilars.

Conclusions: This meta-analysis showed no differences in clinical efficacy between biosimilar and reference G-CSF in breast cancer patients.

Legal entity responsible for the study: n/a

Funding: None

Disclosure: A. Krendyukov: Employee of Hexal AG G. Curigliano: Honoraria from Pfizer, Roche, Sandoz. All other authors have declared no conflicts of interest.

<table>
<thead>
<tr>
<th>Study and year of publication</th>
<th>Reference G-CSF</th>
<th>Biosimilar G-CSF</th>
<th>Mean</th>
<th>No. of patients</th>
<th>Mean</th>
<th>No. of patients</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blackwell 2015</td>
<td>Filgrastim</td>
<td>Filgrastim</td>
<td>1.17</td>
<td>107</td>
<td>1.2</td>
<td>107</td>
<td>14.2%</td>
<td>-0.03 [-0.32, 0.26]</td>
</tr>
<tr>
<td>Blackwell 2016</td>
<td>Pegfilgrastim</td>
<td>Pegfilgrastim</td>
<td>1.36</td>
<td>155</td>
<td>1.19</td>
<td>153</td>
<td>20.2%</td>
<td>0.17 [0.07, 0.41]</td>
</tr>
<tr>
<td>Del Giglio 2008</td>
<td>Filgrastim</td>
<td>Pegfilgrastim</td>
<td>1.1</td>
<td>140</td>
<td>1.1</td>
<td>136</td>
<td>6.4%</td>
<td>0.00 [0.43, 0.43]</td>
</tr>
<tr>
<td>Harbeck 2016</td>
<td>Pegfilgrastim</td>
<td>Pegfilgrastim</td>
<td>0.75</td>
<td>155</td>
<td>0.83</td>
<td>155</td>
<td>28.1%</td>
<td>-0.08 [-0.28, 0.12]</td>
</tr>
<tr>
<td>Park 2016</td>
<td>Filgrastim</td>
<td>Pegfilgrastim</td>
<td>2.28</td>
<td>36</td>
<td>2.08</td>
<td>38</td>
<td>5.6%</td>
<td>0.20 [0.26, 0.66]</td>
</tr>
<tr>
<td>Waller 2010</td>
<td>Filgrastim</td>
<td>Pegfilgrastim</td>
<td>1.6</td>
<td>165</td>
<td>1.3</td>
<td>85</td>
<td>13.4%</td>
<td>0.30 [0.01, 0.59]</td>
</tr>
<tr>
<td>Waller 2016</td>
<td>Pegfilgrastim</td>
<td>Pegfilgrastim</td>
<td>1.2</td>
<td>127</td>
<td>1.2</td>
<td>67</td>
<td>12.2%</td>
<td>0.00 [0.31, 0.51]</td>
</tr>
</tbody>
</table>

Pooled estimate (95% CI): 885 741 100% 0.06 [-0.05, 0.17]

Heterogeneity: Chi² = 6.27 (P = 0.39), I² = 4% *Days with absolute neutrophil count less than 0.5 x 10⁹/L (<500/μL)
Conclusions: The clinical program confirmed the biosimilarity of RGB-02 and Neulasta in highly sensitive clinical study settings. PK comparability of RGB-02 and Neulasta was demonstrated at the clinical dose of 6 mg. PD comparability of RGB-02 and Neulasta was shown at the clinical dose of 6 mg and the reduced dose of 3 mg. The safety and immunogenicity profile of RGB-02 did not show any clinically meaningful differences to Neulasta.

Clinical trial identification: NCT02912377 NCT02629562

Legal entity responsible for the study: Cinia Biotech S.L., Olloki, Spain

Funding: Cinia Biotech S.L., Olloki, Spain

Disclosure: K. Roth, H. Weissel, R. Jankowski: Employee of Cinia Biotech J. Hoefler: Employee of Staburo GMBH, statistical consultancy

### 1575P

**Efficacy and safety of RGB-02, a proposed biosimilar pegfilgrastim to prevent chemotherapy-induced neutropenia: Results of a randomized, double-blind, phase III clinical study vs. reference pegfilgrastim in patients with breast cancer receiving docetaxel/doxorubicin**

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**Background:** Treatment with recombinant human granulocyte-colony stimulating factor (G-CSF) is accepted standard for prevention of chemotherapy-induced neutropenia. RGB-02, a pegylated G-CSF (pegfilgrastim) developed by Gedeon Richter is a proposed biosimilar to the reference pegfilgrastim product Neulasta. Here we are presenting the results of a randomized, comparative, double-blind, multicenter study to evaluate efficacy and safety of RGB-02 in breast cancer patients receiving cytotoxic regimens (EudraCT nr: 2013-003166-14).

**Methods:** 239 women presenting with breast cancer were randomized to RGB-02 (n = 121) and to the reference pegfilgrastim, Neulasta1 (n = 118). All patients received up to 6 cycles of docetaxel/doxorubicin and a once-per-cycle injection of a fixed 6 mg dose of pegfilgrastim. Primary endpoint was the duration of severe neutropenia (ANC < 0.5 x10^9/L) in Cycle 1 (2-sided CI interval 95%). Secondary endpoints included incidence and duration of severe neutropenia, incidence of febrile neutropenia, time to ANC recovery, depth of ANC nadir, and safety outcomes.

**Results:** The mean duration of severe neutropenia in Cycle 1 was 1.7 (RGB-02) and 1.6 (reference), with a difference (LS Mean) of 0.1 days (95% CI -0.2, 0.4). Therapeutic equivalence could be established as the CI for the difference in LS Mean lay entirely within the pre-defined range of ±1 day. The incidence of severe neutropenia decreased from cycle 1 to 2 in both groups with no statistical significant differences, for RGB-02 from 84.6% (99 patients) to 74.4% (60 patients) and from 77.9% (87 patients) to 43.7% (45 patients) in the comparator group. Both groups were similar regarding mean time to ANC recovery with 3.4 ± 1.84 days (RGB-02) and 3.7 ± 1.88 days (reference) during Cycle 1. Safety profiles were comparable between groups.

**Conclusions:** Therapeutic equivalence and similar safety profiles between RGB-02 and Neulasta1 as once-per-cycle administration could be demonstrated. RGB-02 can provide a biosimilar alternative for the prevention of neutropenia.

**Clinical trial identification:** EudraCT nr: 2013-003166-14

**Legal entity responsible for the study:** Gedeon Richter Plc.

**Funding:** Gedeon Richter Plc.

**Disclosure:** K. Horvat-Karazaj, A. Illes: Employee of Gedeon Richter Plc. All other authors have declared no conflicts of interest.

### 1575P

**Impact of resistance exercise on metabolic syndrome (MetS) parameters in men receiving androgen deprivation therapy (ADT) for prostate cancer**

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**Background:** Cardiovascular disease is the leading cause of death in men with prostate cancer. ADT is effective treatment, but can adversely impact MetS components, which may contribute to excess cardiac risk. We tested whether a resistance exercise program, designed to increase skeletal muscle mass during ADT, could offset adverse changes. Methods: Prostate cancer patients on ADT were randomized to exercise (EX) or no exercise (noEX). EX was supervised, periodized resistance training followed by stretching 3x/week for 12 weeks, 45 min/session. noEX did home-based stretching 3x/week. Baseline and post-intervention measurements included weight, waist circumference (wCirc), lean body mass, lipids, insulin, glucose. Mean differences in changes were compared with intent-to-treat linear regression models adjusted for baseline values. Cohen’s D effect sizes were calculated for these pilot data to estimate effects for a fully powered trial.

**Results:** Thirty-two men (EX n = 13, noEX n = 19) completed the protocol. Age (mean ± SD) was 67.3 ± 8.7 years (range 52 - 84). Mean duration ADT was 14 ± 13.4 months (range 3 – 57). EX patients had higher baseline BMI with 63% > 25 kg/m2 compared to 25% in the noEX group, p = 0.024. wCirc decreased significantly (p = 0.032) in EX (-1.18 cm 95%CI [-3.3, -1.0] cm) compared to noEX (+1.97 cm 95%CI [3.0, 2.3] cm). Lean mass increased and body fat decreased in EX compared to noEX. Moderate effect sizes (D = 0.2-0.5) were seen between other groups for other parameters (see Table).

**Conclusions:** Supervised resistance exercise for 12 weeks improves wCirc and body composition in men receiving ADT for prostate cancer with moderate effect on other MetS parameters.

**Clinical trial identification:** NCT01909440

**Legal entity responsible for the study:** University of Southern California, Keck School of Medicine

**Funding:** National Strength and Conditioning Association, California State University Chancellor’s Doctoral Incentive Program

**Disclosure:** All authors have declared no conflicts of interest.

### 1576P

**Body mass index (BMI), lifestyle behaviors, and perceptions in cancer survivors**

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**Background:** Obesity is associated with poorer outcomes across multiple cancer types. Lifestyle behaviours (smoking, physical activity (PA) and alcohol) can improve outcomes among cancer survivors.

**Methods:** Cancer patients of all subtypes were cross-sectionally surveyed on their smoking, alcohol and PA levels, and their perceptions of these behaviours on quality of life.
life (QoL), fatigue and survival (OS). Multivariable logistic regression models evaluated the association of BMI 1 year prior to diagnosis with behaviour changes and perceptions.

Results: Of 1269 patients, 205 smoked at diagnosis and 44% quit at 1 year; 350 (at diagnosis) and 238 (at follow-up) met PA guidelines; 661 drank alcohol at diagnosis with 50% reduced consumption after. Median BMI was 25.8 (22.6% obese); 75% of patients perceived PA as improving QoL and OS, while 34% described smoking and 55% described alcohol consumption as improving QoL and OS. At diagnosis, increased BMI was associated with ex-smoking (vs current smoking; P = 0.003), never using alcohol (vs former user; P = 0.05) and not meeting PA guidelines (P = 0.01). Among smokers at diagnosis, increased BMI was associated with smoking cessation (aOR = 1.08 per 1 unit BMI, P = 0.05) and perceptions that smoking worsens OS (aOR = 1.10, P = 0.04) and fatigue (aOR = 1.08, P = 0.08). Among those not meeting PA guidelines at diagnosis, increased BMI was associated with perceptions that PA worsens fatigue (OR = 1.02, P = 0.06) and is unsafe (OR = 1.04, P = 0.06), but were not associated with PA levels changes after diagnosis. Among drinkers at diagnosis, increased BMI was associated with perceiving alcohol to be less harmful (aOR = 0.95, P = 0.002) and less likely to worsen OS (aOR = 0.96, P = 0.04) and fatigue (aOR = 0.97, P = 0.09), but not with alcohol use changes after diagnosis. BMI was not associated with counselling rates; however, 66% of current smokers received cessation counselling while only 14% of current drinkers and 13% of those not meeting PA guidelines received counseling on their respective behaviours.

Conclusions: Obese patients were more likely to quit smoking and perceive it to be harmful but less likely to perceive alcohol as harmful. Survivorship programs should consider focusing on PA and alcohol counselling in obese patients.

Legal entity responsible for the study: Princess Margaret Cancer Centre

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Disclosure: All authors have declared no conflicts of interest.

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Background: Awareness of the importance on exercise and dietary intervention can provide significant benefits for lung cancer patients and survivors. This study first aimed to identify the barriers and preferences to improving awareness of the importance on exercise and dietary education. In addition, the study also explored the perceptions of patients’ awareness of the importance on exercise and diet education toward the stage of behavior change, intention of actual participation to the programs.

Methods: A total of 830 lung cancer survivors from two hospitals in South Korea participated in this postal questionnaire-survey. Standardized measures including patients’ sociodemographic variables, preferences for appropriate education time and place were identified as the barriers for their awareness of the importance of exercise and diet counseling program. In addition, the impacts of it on each intention of actual participation to both programs and maintaining regular exercise and balanced diet were analysed in order.

Results: Patients who recognized exercise education program very important had more intention of actual participation to the program (adjusted Odds Ratio [aOR] 2.11; 95% Confidential Interval [CI], 1.57-2.83). In addition, subjects who recognized diet counseling programs very important maintained their behavior of balanced diet more than 6 months (aOR 2.57; 95% CL, 1.92-3.61). However, significant differences based on the socio-demographic variables and program preferences (i.e., lower education and income, preferred time and place etc.) were identified as main barriers for survivors’ awareness of the importance of the exercise and diet counseling program.

Conclusions: Identification of main barriers provides valuable information regarding improving survivors’ awareness of the importance on exercise and dietary intervention, which should be targeted in maintaining future physical activity and balanced diet, and encouraging the intention of actual engagement to the programs.

Legal entity responsible for the study: Ministry of Health & Welfare, Republic of Korea

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Disclosure: All authors have declared no conflicts of interest.

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Background: Inhibition of the epidermal growth factor receptor (EGFR) extends patient survival in multiple tumor types. However, EGFR inhibition is associated with skin toxicities such as mild to moderate acneiform rash, which can be severe in up to 18% of patients. A previously performed structured literature search revealed an unmet need for research regarding the influence of dermatologic adverse events (dAEs) on patients' quality of life (QoL), patient acceptance of cancer treatments, and economic-risk/benefit tradeoff from the patients’ perspective. This survey reports on these topics in patients who received the anti-EGFR monoclonal antibody cetuximab.

Methods: Using a multinational survey that included 195 patients, we conducted a sub-analysis of 66 patients who previously received cetuximab-based cancer therapy (44 with metastatic colorectal cancer [mCRC] and 22 with squamous cell carcinoma of the head and neck [SCCHN]) to gauge attitudes regarding skin toxicities.

Results: 64/66 patients (96/94 with mCRC and 21/22 with SCCHN) experienced dAEs. Skin toxicities were cited as causing pain and physical discomfort as well as impairing QoL. Despite the negative social, physical, and functional impacts of dAEs, 70% of patients with mCRC and 64% of patients with SCCHN who received cetuximab stated that they would prefer a more efficacious cancer therapy that induced more severe skin reactions as the outcome of a more efficacious cancer therapy. Furthermore, in an efficacy-safety tradeoff exercise, nearly two-thirds of patients (65%) stated that they would accept a new therapy with improved efficacy, even if it caused severe skin reactions in 1 out of every 2 patients experienced a severe skin rash on this therapy.

Conclusions: Patients with mCRC or SCCHN who previously received the anti-EGFR antibody cetuximab as part of their cancer therapy were willing to accept skin toxicities as an AE if these toxicities were the anticipated byproduct of a more effective therapeutic regimen.

Legal entity responsible for the study: Merck KGaA, Darmstadt, Germany

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Background: Malnutrition and cachexia occur in most cancer patients (pts) impacting quality of life (QoL) and anticancer treatment (Tx) outcomes. Nutritional care can help reverse weight loss and improve pt outcomes; however, previous surveys at ESMO (2014, 2015) suggest nutritional care/assessment is insufficiently implemented in clinical practice, despite educational and academic efforts.

Methods: This survey created by the authors, including questions from prior surveys, was compiled by ESMO 2016 delegates visiting the Nutricia booth.

Results: Of 2,011 respondents, 78% were medical oncologists, 56% were Europe based; 61% always discuss nutritional aspects during multidisciplinary tumor boards. To address malnutrition, 44% measure weight, 30% evaluate systemic inflammation, and 14% assess muscle mass. Eligibility of pts to receive nutritional support is assessed before (48% in 2015, 45% in 2014) or during (54%) initiation of anticancer Tx, at primary diagnosis (28%), if weight loss is visible during outpatient visits (42%), and when anticancer Tx ends (26%). Main impacts of malnutrition are increased anticancer Tx toxicity (58%; 2015: 53%; 2014: 53%), surgery/radiation therapy complications (40%; 37%), anticancer Tx discontinuation/decreased effectiveness (54%; 40%; 40%), decreased QoL (58%; 56%; 54%), impaired physical function (47%; 44%; 45%), or distress of family members (35%; 32%; 32%). Main goals of nutritional support include QoL (65%; 69%; 64%), completion of anticancer Tx (54%; 52%; 45%), or stabilizing weight (48%; 44%; 47%). Popular approaches to minimize weight loss are anorectics (48%; 56%), appetite stimulants (41%; 48%), more-effective anticancer Tx (39%; 47%), anti-cachexia drugs (38%; 45%), and timely and individually tailored dietary advice (36%). During systemic Tx, 83% apply physical exercise programs (either alone or in combination with nutritional care).

Conclusions: Compared with our previous surveys, awareness and assessment of malnutrition in cancer pts seems slightly increased. HCPs recognize impacts of malnutrition but may need better guidance on how to improve nutritional care in the supportive and palliative setting.

Legal entity responsible for the study: Nutricia Advanced Medical Nutrition

Funding: Nutricia Advanced Medical Nutrition

Disclosure: F. Strasser: Funds from: Acacia ACRAF Amgem Baxter Celgene Danone Fresenius GSK Grünenthal Hemlin IsisGlobal Millennium/Takeda Mundipharma Novartis Novo Nordisk OxyFrench Otsuka Pfizer Pharm-Olam PrMe Sanhera Sunstone Teva Vifor. Other substantive relationships: independent talk at industry sponsored educational/scientific events N. Georgiou: Corporate-sponsored researcher; employee of Nutricia Advanced Medical Nutrition M. Sawyer: Other substantive relationships: honoraria from Nutricia for presentations, honoraria from Fresenius Kabi for presentations S. Kasa: Stock ownership: Eir solution As all other authors have declared no conflicts of interest.

A survey of patient acceptance of skin toxicities from cetuximab-based therapy
Background: Proton pump inhibitors (PPIs) may interact with several orally administered drugs, possibly by raising gastric pH levels, leading to altered dissolution and absorption. In a previous study, we found that co-administration of PPIs with cetuximab was associated with increased skin toxicity. To confirm this preliminary observation, we tested this observation retrospectively. Since both these drugs can induce hypomagnesemia, the possibility of synergism between them was also tested.

Methods: The files of patients with metastatic colorectal carcinoma (mCRC) or head and neck (H&N) carcinoma treated at our center with cetuximab as a single agent or in combination with chemotherapy or radiotherapy were reviewed. All eligible patients treated with cetuximab during 2013 and 2016 were included in the study. The concomitant use of PPIs was defined if a drug belonging to that class was included in the patient’s chronic medications list.

Results: One hundred eighteen patients (61 with H&N carcinoma, 57 with mCRC) were treated with cetuximab. Skin toxicity of any grade was reported in 33/58 (56.9%) patients on PPIs compared with 22/60 (36.7%) patients not on PPIs (p = 0.08). Grade 3-4 skin toxicity was reported in 19/58 (32.8%) patients on PPIs compared to 2/60 (3.3%) not on PPIs (p = 0.001). Median time to detection of severe skin toxicity was 0.7 months [range, 0.2-11.0 months]. Hypomagnesemia (Mg serum level < 0.9mg/dL) was reported in 14/58 (25.9%) PPI treated patients compared with 5/60 (10%) patients not on PPIs as a chronic medication (p = 0.08). Median time to detection of hypomagnesemia was three months [range, 0.4-52.8 months]. Complications of all grade skin toxicity or hypomagnesemia were reported in 40/58 (69%) patients on PPIs compared to 23/60 (38.3%) patients not on PPIs (p = 0.04). Grade 3-4 skin toxicity or hypomagnesemia (Mg < 0.9mg/dL) were reported in 23/58 (39.7%) patients on concomitant treatment with PPIs compared with PPIs treated without PPIs (p = 0.03).

Conclusions: Both the rate and the severity of cetuximab-induced skin toxicity and hypomagnesemia were increased by chronic concomitant administration of PPI. A prospective study is needed to confirm the possible interaction between cetuximab and PPIs.

Legal entity responsible for the study: Mahmoud Abu Amna

Disclosure: All authors have declared no conflicts of interest.

1582P
NeuroCog-FX study: A multicenter cohort study on cognitive dysfunction in patients with early breast cancer

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Background: Autonomic neuropathy in geriatric patients with gynecologic cancer receiving taxanes and platinum chemotherapy

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Background: The standard of care for ovarian cancer in elderly is using paclitaxel and carboplatin, an effective and efficient combination, but has serious toxicities. Peripheral neurotoxicity is one of the commonest toxicities which are seen occurring in 60% to 90% of patients. It is debilitating and vexing. Unfortunately, there is very little or no data regarding autonomic neuropathy in this setting. This study is an attempt to highlight this problem.

Methods: Single center cohort study of patients for the period 2013-2015. All patients were above the age of 65 years. 88 patients were included. The other were for autonomic neuropathy using standard forms and methods including positional and stereotonic sense for neuropathy. NCI scales of grading peripheral neuropathy were followed. Autonomic neuropathy assessments were done by cardovascular autonomic reflex test and gastro-intestinal autonomic neuropathy by using gastric phase emptying test. Genito-urinary autonomic neuropathy was tested for erectile dysfunction and bladder dysfunction. The tests were administered at baseline after 2nd, 4th and 6th cycle of one of the patient complained of suggestive symptoms.

Results: 37% of patients developed grade 3/4 peripheral neuropathy. 59% of patients developed symptomatic autonomic neuropathy. Cardio vascular autonomic neuropathy occurred in 30% while gastric neuropathy was seen in 19%. Combined was seen in 16%. Constipation, diarrhea and reeling of head was the most common complaint. Autonomic neuropathy was more common in diabetes 60% vs 48% (p > 0.05). Attempts to intervene using pharmacotherapy methods and non-pharmacotherapy methods were attempted.

Conclusions: Autonomic neuropathy seems to be common in geriatric population treated by this drug combination although there is not much mention either in real life or in clinical trials or if available as data contributed to other causes. Caution must be exerted in patients in diabetics and proper screening should be done in this patient population for autonomic neuropathy and peripheral neuropathy.

Legal entity responsible for the study: G.S. Bhattacharyya

Disclosure: None

Disclosure: All authors have declared no conflicts of interest.

1586P
Potential drug interactions in older patients with cancer: Updated data from the ELCAPA cohort survey

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Background: Because of polypharmacy, older cancer patients are at risk of adverse events related to potential drug interactions (PDI). We aim to identify PDI in daily medications, between daily medications and chemotherapy (CT), and related potential clinical outcomes (PCO).

Methods: All cancer patients aged ≥70 years, referred for geriatric assessment at Henri Mondor Hospital (Paris’ area, Creteil, France), included in the prospective ELCAPA cohort survey (2007–2014), and who received CT were included. PDI were identified using Lexicomp® (LexComp, Hudson, USA) and Cerner®. All the PDI were classified as: A, no interactions; B, no action needed; C, monitor therapy; D, consider therapy modification; X, avoid combination. Factors associated with grade C or D/X PDI were analyzed using ordered multivariate logistic regression.

Results: We analyzed 442 patients (median age: 78 years; 49% women). Main tumor sites were upper digestive tract (23%), colorectal (21%), urological tract (19%), lymphoid malignancies (15%), and breast (12%); 23% had metastasis. Median number of drugs/patients/day was 1 (Q1-Q3 = 1-4). We identified 1742 PDI: 87% in daily medications (183 patients had grade C PDI (41%), 128 grade D/X PDI (29%), and 13% between daily medications and CT (66 patients had grade C PDI (15%), 56 grade D/X PDI (13%). Main PCO involving daily medications were: hypotension risk (33%), psychotropic effects (17%), glycemic (12%) and hemostasis (9%) dysregulations. Main PCO related to PDI involving CT were risk of CT over-exposure (34%), hypotension risk (20%), and hemostasis dysregulation (11%). In multivariable analysis, adjusted for depression and reduced quality of life. Neither tumor therapy nor other clinical parameters had a significant impact on development of CD.

Legal entity responsible for the study: Frankfurt

Disclosure: None

Disclosure: All authors have declared no conflicts of interest.
number of drugs, factors associated with grade D/X PDI, both with or without CT were ≥2 metastatic sites (p = 0.01) and lymphoid malignancies (p = 0.01). Patients living alone had less grade D/X PDI in daily medications (p = 0.003), while breast cancer (p = 0.04) was associated with grade D/X PDI in daily medications. Higher body mass index was associated with grade D/X PDI involving CT (p = 0.03).

Conclusions: The high prevalence of PDI in older cancer patients highlights the need to assess precisely the iatrogenic risk before anti-cancer treatment.

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Disclosure: All authors have declared no conflicts of interest.

1587P Enhanced supportive care in early phase clinical trials

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Background: Enhanced Supportive Care (ESC) is a fresh approach to supporting patients through cancer treatment and recognised nationally by NHS England. The Supportive Care Team (SCT) and Experimental Cancer Medicine Team (ECMT) at the Christie Hospital applied the validated ‘Integrated Palliative care Outcome Scale’ (IPOS; http://pos-pal.org/) in a pilot study examining the impact of ESC for patients (pts) entering early phase clinical trials. The main aims of this study were to maximise patient recruitment and retention and enhance the patient experience within the context of experimental cancer medicine clinical trials.

Methods: The IPOS tool was used to assess the effect of ESC on patient outcomes in pts on an ECMT trial. It was administered by the SCT healthcare professionals to any pts with baseline symptoms thought to be related to their underlying cancer diagnosis and at all pt visits as per trial protocol. Analysis is based on patient data where both an initial and subsequent form had been completed. Two aspects of the IPOS tool were reviewed: the overall IPOS score, the score for all symptoms as a whole and individual pain score.

Results: Data was collected from 24 pts within ECMT trials during a four-month period in 2016. The mean age was 56 years (31 to 79); 10 male and 14 female. Performance status at initial assessment was 0 (3 pts); 1 (18 pts); 2 (1 pt); unknown (2 pts). 16 pts had no previous contact with SCT services. The commonest reason for referral to the SCT was for optimisation of pain control (24/24 pts) followed by general symptom control (8/24) and psychological issues (2/24). 21 pts were seen on the day of referral, 3 pts seen >8 days of referral. 16/24 pts (67%) reported improvement in pain (and IPOS scores) within 4 weeks and 17/24 pts (71%) reported improvement in overall symptom control within 4 weeks.

Conclusions: This study has demonstrated the effectiveness of ESC on the outcomes of patients being reviewed by the SCT on ECMT clinical trials. There were considerable reductions in the overall IPOS scores and in pain score specifically. ESC has now been adopted into routine practice by our ECMT, and we are the first unit to do so in the UK. We next plan to measure the impact of ESC on patient experience, adverse events on trials, hospital admissions and treatment duration.

Legal entity responsible for the study: Experimental Cancer Medicine and Enhanced Supportive Care Team

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Table: 1587P

<table>
<thead>
<tr>
<th>CPG AWARENESS</th>
<th>AGREEMENT</th>
<th>IMPLEMENTATION (in medical records)</th>
<th>IMPLEMENTATION (ranked drug of choice characteristics)</th>
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</thead>
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<tr>
<td>SEOM 97.1%</td>
<td>100% documentation</td>
<td>Episodes (n) 73.5%</td>
<td>Rapid onset</td>
</tr>
<tr>
<td>ESMO 63.2%</td>
<td>99% best evidence</td>
<td>Pain intensity 66.3%</td>
<td>High potency</td>
</tr>
<tr>
<td>NCCN 58.8%</td>
<td>99% specific medication</td>
<td>Duration 45.8%</td>
<td>Short duration</td>
</tr>
<tr>
<td>Instt 19.1%</td>
<td>99% fentanyl 1st choice</td>
<td>Time to peak 30.1%</td>
<td>Route of administration</td>
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<tr>
<td>Other 7.3%</td>
<td></td>
<td>Triggers 75.9%</td>
<td>Ease of use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Relief strategies 73.5%</td>
<td>Minimum side effects</td>
</tr>
<tr>
<td></td>
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<td>Etiopathogenesis 86.7%</td>
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Background: Lifestyle behaviors including smoking cessation, physical activity (PA) and alcohol moderation are important aspects of a cancer survivorship program. We assessed cancer patient (pt) interest and perceptions of programs for these behaviours.
Results: At diagnosis, 115 pts smoked; 41% had second hand smoke (SHS) exposure; 238 were drinking alcohol, 313 did not meet PA guidelines. At risk individuals (e.g., smokers for smoking cessation, exposed to SHS for household smoking cessation) surveyed results are shown in the table. Preceptions of how these behaviors impact quality of life, survival and fatigue was not associated with program interest (P > 0.05). However, pts perceiving that alcohol worsened and PA improved these outcomes were more likely to believe these programs are beneficial (alcohol aORs = 2.1-2.2 P < 0.03; PA aORs = 1.9-3.2 P < 0.02) and should be routine care (alcohol aORs = 1.9-3.5 P < 0.03; PA aORs = 1.7-2.4 P < 0.01). Pts with more pack-yrs less likely perceived benefit in a household cessation program (aOR = 1.02 P < 0.007) or in a routine care program (aOR = 1.01 P < 0.02). Pts preferred discussing programs with doctors (35%+) or counsellors (42%+).

Conclusions: About half of pts feel that lifestyle behavior programs would be beneficial and should be part of routine care. These factors were more important than perception of the behaviors on outcomes in influencing pt interest. Initial discussions with pts should focus on discussing benefits of these programs.

Legal entity responsible for the study: Princess Margaret Cancer Centre

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Table: 1590P

<table>
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<tr>
<th>Program</th>
<th>% at risk interested in program</th>
<th>Believe Program is Beneficial</th>
<th>Believe in Routine Care Program</th>
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<tbody>
<tr>
<td></td>
<td>Agree</td>
<td>aOR of being interested (95% CI) P</td>
<td>Agree</td>
</tr>
<tr>
<td>Smoking Cessation</td>
<td>53%</td>
<td>57%</td>
<td>2.85 (1.0-7.9) 0.04</td>
</tr>
<tr>
<td>Household Smoking Cessation</td>
<td>37%</td>
<td>55%</td>
<td>2.73 (1.1-6.7) 0.03</td>
</tr>
<tr>
<td>PA</td>
<td>53%</td>
<td>70%</td>
<td>4.73 (2.5-9.0) &lt; 0.001</td>
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<tr>
<td>Alcohol Moderation</td>
<td>25%</td>
<td>55%</td>
<td>2.54 (1.3-5.1) 0.01</td>
</tr>
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</table>

Legal entity responsible for the study: National Cancer Center Hospital East

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1591P

Hepatitis B and C reactivation rates due to cytotoxic chemotherapy in patients with solid tumors

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Background: We tried to determine the incidence of the reactivation rates of chronic HBV and HCV infections in cancer patients who received different types of chemotherapy or immunosuppressive therapy. Also we tried to identify the chemotherapy regimens though to be associated with this reactivation of chronic HBV and HCV infections.

Methods: Between 2008 and 2014, 8322 cancer patients who were admitted to oncology departments were evaluated retrospectively and 3890 patients in whom hepatitis serology were available were included in this study. Their mortality rates, chemotherapy regimens, cancer types, number of positive hepatitis serology and reactivation rates were also obtained.

Results: In all 8322 cancer patients, only 3890 (47%) patients had hepatitis serology results and 355 patients had positive hepatitis serology results (HBsAg, anti-HBcAg, anti-HCV). Of them, 4.24% had anti-HBcAg positivity, 3.65% had HBsAg positivity, and 1.23% had anti-HCV positivity. Nineteen patients with HBsAg positive (13.38%), 4 patients with anti-HBcAg positive (2.42%), and 2 patients with anti-HCV positive (4.16%) had reactivation. hepatitis reactivation was seen significantly higher in lymphoma patients (p = 0.032). Reactivation rate of hepatitis B in those patients (HBsAg positive) was detected as 57.14%. In patients with hepatitis reactivation, the rates of usage of 5-FU, cisplatin, cyclophosphamide, doxorubicin, steroid, rituximab, and vincristine was detected as significantly higher than patients with positive hepatitis serology results but without hepatitis reactivation (p > 0.05 for all).

Conclusions: An association between hepatitis reactivation and the usage of 5-FU, cisplatin, cyclophosphamide, doxorubicin, steroid, rituximab, and vincristine was determined. Thus physicians should consider antiviral prophylaxis before initiating these chemotherapies.

Legal entity responsible for the study: Individuals: Ahmet Ozet, Deniz Tural

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Methods: 501 cancer pts from all subtypes were surveyed on their smoking, PA and alcohol consumption patterns along with their interest and perceptions for programs for these behaviors. Multivariative logistic regression models identified factors associated with pt interest and perceptions.

Results: At diagnosis, 115 pts smoked; 41% had second hand smoke (SHS) exposure; 238 were drinking alcohol, 313 did not meet PA guidelines. At risk individuals (e.g., smokers for smoking cessation, exposed to SHS for household smoking cessation) survey results are shown in the table. Preceptions of how these behaviors impact quality of life, survival and fatigue was not associated with program interest (P > 0.05). However, pts perceiving that alcohol worsened and PA improved these outcomes were more likely to believe these programs are beneficial (alcohol aORs = 2.1-2.2 P < 0.03; PA aORs = 1.9-3.2 P < 0.02) and should be routine care (alcohol aORs = 1.9-3.5 P < 0.03; PA aORs = 1.7-2.4 P < 0.01). Pts with more pack-yrs less likely perceived benefit in a household cessation program (aOR = 1.02 P < 0.007) or in a routine care program (aOR = 1.01 P < 0.02). Pts preferred discussing programs with doctors (35%+) or counsellors (42%+).

Conclusions: About half of pts feel that lifestyle behavior programs would be beneficial and should be part of routine care. These factors were more important than perception of the behaviors on outcomes in influencing pt interest. Initial discussions with pts should focus on discussing benefits of these programs.

Legal entity responsible for the study: Princess Margaret Cancer Centre

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1590P

The investigate relationship between severe neutropenia and ABCB1 and ABCG2 gene polymorphisms with esophageal cancer patients receiving docetaxel, cisplatin and 5-fluorouracil chemotherapy

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Background: The combination of docetaxel, cisplatin and 5-fluorouracil (DCF) is a newly developed chemotherapy for esophageal cancer patients (pts). Severe neutropenia is one of the major adverse events that necessitate chemotherapy dose reduction. This study aimed to investigate relationship between grade 3 and 4 neutropenia and genetic polymorphisms in EC pts receiving DCF.

Methods: EC pts who had undergone DCF chemotherapy at National Cancer Center Hospital East from August 2011 to December 2016 were enrolled in this study. Prophylactic administration of granulocyte-colony stimulating factor was not conducted for the all EC pts during the above chemotherapy. Seven polymorphisms in the genes encoding docetaxel-metabolizing enzymes and transporters were genotyped, and then relationship between these genotypes and the grade 3 and 4 neutropenia was then investigated. Risk factors that enable to predict grade 3 and 4 neutropenia after first cycle of chemotherapy were explored using multivariative logistic regression analysis.

Results: A total of 170 pts treated with DCF were enrolled in this study period. The median age was 64 years, median body mass index was 22.0 (15.3 - 31.0), median serum hemoglobin level was 13.3 (8.7 - 17.1) g/dL, median prognostic nutritional index was 50.1 (36.7 - 68.7) and baseline absolute neutrophil count (ANC) was 4305 (1660 - 11020)/mm3. The proportion of pts with grade 3 and 4 neutropenia was 56 (32.9%) and 34 (21.2%), respectively. Multivariative logistic regression analysis adjusted for potential risk factors revealed ABCB1 3435 C > T (p = 0.015), ABCG2 34 G > A (p = 0.044), age (60+) (p = 0.001) and baseline ANC (< 4305) (p = 0.001) were independent and significant risk factors for grade 3 and 4 neutropenia.

Conclusions: We identified that genetic polymorphisms in ABCB1 3435 C > T and ABCG2 34 G > A was a significant predictor for grade 3 and 4 neutropenia of EC pts receiving DCF.
The preventive role of intravenous L-lactyl L-glutamine in reducing the incidence of oral mucositis in head and neck cancer patients receiving radiotherapy with or without chemotherapy

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Clinical Oncology and Nuclear Medicine, Tanta University Hospital, Tanta, Egypt

Background: The current prospective comparative phase 2 study aimed to assess the role of intravenous L-lactyl L-glutamine in reducing the rate of oral mucositis for squamous head and neck cancer patients receiving radiotherapy with or without concurrent chemotherapy.

Methods: From September 2014 to September 2016, 100 head and neck cancer patients were treated with radiotherapy or combined chemo-radiation at the Clinical Oncology Department, Tanta University Hospitals. Patients were randomized in a 1:1 ratio into Group A (n = 50 patients) treated by radiotherapy or concurrent chemo-radiotherapy and Group B (n = 50 patients) to receive same treatment in addition to intravenous Glutamine. The investigational drug was infused daily at dose of 0.3-0.6 g/kg diluted in NS and administered at rate of 0.1 g/kg/hr. All patients received total dose of 65-70 Gy using 6MV photon beam supplemented with electron beam when needed. For concurrent chemotherapy, Capcitabin (40mg/m2) was administered weekly.

Results: Mucositis was assessed by WHO grading system. A significantly higher incidence of mucositis was reported in 45% of Group A patients compared with patients in group B who received glutamine 10% P < 0.001. Group B patients had significantly longer period free from mucositis in comparison to Group A with median time (12 weeks) vs 8 weeks (P < 0.001). A significant reduction in oral mucositis response was reported in group B compared to group A (50% vs 15%) P < 0.001. More Patients needed hospitalization in group A (20%) vs (5%) in group B P = 0.059. No adverse effects were observed in relation to glutamine.

Conclusions: Intravenous L-lactyl L-Glutamine may be an effective measure to lower incidence or prevention of oral mucositis in head and neck cancer patients treated by radiotherapy or combined chemo-radiotherapy.

Legal entity responsible for the study: Tanta University Hospital

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1594P
Biosimilar epoetin alfa (HX575) for the treatment of chemotherapy-induced anaemia: Development, approval and 10 years' clinical experience

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Background: Patent expirations for biological products have prompted the development of biosimilars, which have comparable quality, safety and efficacy to a licensed biological medicine (the ‘reference’ medicine). HX575 (Biocinn®), epoetin alfa biosimilar, was approved in Europe in 2007 for the treatment of chemotherapy-induced anaemia (CIA).

Methods: The development and approval of HX575 included extensive analytical characterisation and comparison with the reference epoetin alfa, followed by a clinical development programme; this included phase I pharmacokinetic/pharmacodynamic studies to show bioequivalence to the reference medicine, and a confirmatory phase III study to confirm therapeutic effectiveness in CIA. Since approval, HX575 has been extensively used in real-world clinical practice.

Results: An array of analytical methods confirmed the similarity of HX575 and the reference epoetin alfa in terms of primary protein structure, higher-order protein structure, isoform pattern, post-translational modifications, receptor binding and biological activity. Phase I studies showed that HX575 and the reference medicine were bioequi- valent following intravenous and subcutaneous administration. In a confirmatory phase III study (n = 114), HX575 was effective in treating CIA in cancer patients, and had a safety profile consistent with the therapeutic class and as expected for the therapeutic area. Post-approval data are also available for a range of cancer types; positive results have been reported from a multi-centre retrospective clinical study, single-centre experiences from several countries, and a large-scale prospective observational study. No additional unexpected safety issues have emerged after 10 years of pharmacovigilance. A pilot study has suggested that HX575 may also be effective for the treatment of anaemia in low-intermediate I risk myelodysplastic syndromes.

Conclusions: As of Feb 2017, HX575 has generated >252,000 patient years’ experience in CIA worldwide. Accumulated data and experience over a decade are reassuring that...
Experience with the implant of vascular access devices by medical oncologist in a non-surgical scenery

A. Revuelta1, D. Rodriguez Rubi2, M.I. Sánchez Lorenzo3, L. Ruiz Echeverria4, W. Li1, M.F. Sols Fernández1, L. Fáez García1, S. Fernández Amo1, C. Iglesias Gómez1, N. Villanueva Palicio1, P. Jimenez Fonseca2, M. Luque Cabal1, C. Álvarez Fernández1, M. Izquierdo1, J.M. Veítes4, E. Esteban2

1Medical Oncology, Hospital Universitario Central de Asturias, Oviedo, Spain, 2Medical Oncology, Hospital de Burgos, Burgos, Spain, 3Medical Oncology, Hospital de Cabueñes, Gijón, Spain

Background: Totally implantable central venous catheters are widely used in the management of patients (pts) with malignant diseases in order to facilitate drug delivery for the provider for urgent advice thereby reducing unscheduled visits such as emergency room (ER) attendance and hospitalizations which are common during chemotherapy. The aim is for all chemotherapy patients to have access to an oncology care program evaluation for quality improvement purposes. A paper survey was developed. Between September and November 2016, 4 hospitals providing systemic Regional Systemic therapy program

Results: A total of 140 surveys were administered to 32 lung, 38 breast, 39 GI, 22 hematologic and 9 sarcoma patients. Overall, 83% of patients stated they knew where to go to get help for side effects; 56% of patients were told where to get help by a staff member, usually a nurse (44%) or oncolgist (23%), while 19% reported they were not told where to get help by anyone. Across all time points the majority of patients stated they would present to ER for side effect management (41, 76 & 81% respectively). The only exception was the academic hospital where 69% of patients reported calling the clinic/nursing telephone line on weekdays 9am-5pm (comparison between academic and community centers p < 0.001). Qualitative analysis of comments revealed that patients want more resources and education in easily accessible formats and prefer to speak to a person rather than leaving voice messages.

Conclusions: Significant gaps in patient care and education are highlighted by these results. Site specific quality improvement projects are currently underway to address these findings prior to re-administering the survey.

Legal entity responsible for the study: Regional Systemic therapy program

Funding: None

Disclosure: All authors have declared no conflicts of interest.

The effects of nurses’ empathy skills on attitudes towards patients with cancer

A. Alkan

Medical Oncology, Osmangazi Public Hospital, Osmangazi, Turkey

Background: Empathy is sine qua non ability of nurses and the positive effects of empathy on clinical management have been documented. In addition, its positive effects have also been reported in oncology practice. The purpose of this study is to evaluate the predictors of empathy skills and attitude towards cancer patients and association between nurses’ empathy skills on attitudes towards patients with cancer.

Methods: A structured questionnaire was used to evaluate the nurses’ empathy skills and their attitudes towards to patients with cancer. Jefferson Scale of Empathy (JSE) and Attitudes Towards Cancer Scale (ATCS) were used. The predictors of JSE/ATCS scores and correlation between JSE and ATCS were analyzed.

Results: 305 nurses participated in the study (84.2% of all nurses). The median age was 33 (20-52) and most of the nurses were female (82.6%). Most of the participants were married (188, 61.6%) and 40.3% of nurses had an job experience more than 10 years. Female sex, being married, having job experience more than 10 years or caring more cancer patients were associated with higher JSE scores. Nurses caring more cancer patients weekly, experience with cancer patients, participation in educational activities about cancer care or presence of relative with a diagnosis of cancer were found to have more positive attitudes towards cancer patients. Spearman correlation analysis showed a positive, weak correlation between JSE and ATCS (r = 0.017, p = 0.38).

Conclusions: Empathy skills are important while caring patients, especially in oncology practice. Although a direct correlation between empathy skills and attitudes towards cancer patients couldn’t be demonstrated, health care workers caring cancer patients should be both evaluated for empathy skills and educated.

Legal entity responsible for the study: N/A

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Can postponement of death be used in shared decision making in patients treated with adjuvant chemotherapy?

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Background: Standard adjuvant treatment to patients with stage III colon cancer is six months of adjuvant combination chemotherapy with a 5-fluorouracil derivate (5-FU) and oxaliplatin. In some cases, 5-FU monotherapy may be an option. The aim is to develop a different way of explaining the benefit of different treatment options by using the concept of “postponement of death”.

Methods: We identified pivotal phase III publications about adjuvant treatment for stage III colon cancer. Data regarding overall survival was extracted for observation versus 5-FU monotherapy and combination chemotherapy versus 5-FU. Data about the impact of N1 and N2 category was extracted if available. Data was used for restricted mean survival analysis. Postponement of death was defined as the mean difference in survival time between the two randomized treatment arms. Survival curves were plotted

Disclosure: S.M. Aapro: Consulting or Advisory Role: Sandoz

Speakers’ Bureau: Sandoz

None

Legal entity responsible for the study: Sandoz A. Krendyukov, N. Höbel, A. Seidl: Employee of Sandoz International GmbH sponsored events

None

Disclosure:

A. Revuelta1, D. Rodriguez Rubi2, M.I. Sánchez Lorenzo3, L. Ruiz Echeverria4, W. Li1, M.F. Sols Fernández1, L. Fáez García1, S. Fernández Amo1, C. Iglesias Gómez1, N. Villanueva Palicio1, P. Jimenez Fonseca2, M. Luque Cabal1, C. Álvarez Fernández1, M. Izquierdo1, J.M. Veítes4, E. Esteban2

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Legal entity responsible for the study: Regional Systemic therapy program

Funding: None

Disclosure: All authors have declared no conflicts of interest.

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A. Alkan

Medical Oncology, Osmangazi Public Hospital, Osmangazi, Turkey

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Conclusions: Empathy skills are important while caring patients, especially in oncology practice. Although a direct correlation between empathy skills and attitudes towards cancer patients couldn’t be demonstrated, health care workers caring cancer patients should be both evaluated for empathy skills and educated.

Legal entity responsible for the study: N/A

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Can postponement of death be used in shared decision making in patients treated with adjuvant chemotherapy?

N.D. Traberg1, T.F. Hansen1, K.D. Steffensen1, A. Jakobsen1, L.H. Jensen1

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Background: Standard adjuvant treatment to patients with stage III colon cancer is six months of adjuvant combination chemotherapy with a 5-fluorouracil derivate (5-FU) and oxaliplatin. In some cases, 5-FU monotherapy may be an option. The aim is to develop a different way of explaining the benefit of different treatment options by using the concept of “postponement of death”.

Methods: We identified pivotal phase III publications about adjuvant treatment for stage III colon cancer. Data regarding overall survival was extracted for observation versus 5-FU monotherapy and combination chemotherapy versus 5-FU. Data about the impact of N1 and N2 category was extracted if available. Data was used for restricted mean survival analysis. Postponement of death was defined as the mean difference in survival time between the two randomized treatment arms. Survival curves were plotted

Disclosure: S.M. Aapro: Consulting or Advisory Role: Sandoz

Speakers’ Bureau: Sandoz

None

Legal entity responsible for the study: Sandoz A. Krendyukov, N. Höbel, A. Seidl: Employee of Sandoz International GmbH sponsored events

None

Disclosure:
1Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada, 4Department of Radiation Oncology, Princess Margaret Cancer Centre, Toronto, ON, Canada, 5Department of Biostatistics, Ontario Cancer Institute, Princess Margaret Cancer Centre, Toronto, ON, Canada, 6Otolaryngology-Head and Neck Surgery, University of Toronto, Toronto, ON, Canada, 2Department of Biostatistics, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada, 3Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada, 7Addictions, Centre for Addiction and Mental Health, Toronto, ON, Canada

Disclosure: All authors have declared no conflicts of interest.

1599P
Cancer patient attitudes and preferences towards smoking status assessment


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Background: Continued smoking after a cancer diagnosis is associated with poorer outcomes. As smoking cessation is an important part of cancer care, understanding cancer patient (pt) attitudes towards smoking status assessment will help with integrating smoking cessation programs into cancer care.

Methods: Cancer pts from all subtypes were surveyed on their smoking history, assessment rates and attitudes/preferences towards smoking status assessment. Multivariate logistic regression models helped assess for factors associated with screening preferences.

Results: Among 501 pts, 115 smoked at diagnosis and 60% quit after; 53% had a tobacco related (lung/head and neck) cancer (TRC); 64% were treated curatively; 40% received adjuvant, 28% palliative treatment. 12% were assessed at only the first visit (87%). Most preferred being assessed by their oncologist (88%); less than half preferred being asked by another healthcare provider (44%), on paper (29%) or electronic surveys (15%). When compared to ex/never smokers, current smokers were more agreeable (54%) to being assessed every visit compared to head and neck cancer pts (TRC); 36% vs 20% P < 0.001). Among current smokers, lung cancer pts were more agreeable (54%) to being assessed every visit compared to head and neck cancer pts (aOR = 2.45 95% CI [0.9-6.5] P = 0.06) and non TRCs (aOR = 2.63 [1.0-6.8] P = 0.05). Among all pts who were older (aOR = 1.03 [1.0-1.1]), curative (aOR = 1.92 [1.1-3.2]) and smoked less (aOR = 0.98 per płyk [0.97-0.99]) were more agreeable to assessment at each visit.

Conclusions: Most cancer pts felt that assessment of smoking status was important, were comfortable with being assessed and preferred being assessed directly by their oncologist. Routine screening of those currently smoking is recommended to help with cessation.

Legal entity responsible for the study: Princess Margaret Cancer Centre

Funding: None

Disclosure: None

1600P
Optimizing Physician Surveys in Pharmacovigilance Using ecancer Online Community


1Dept of Medicine, CHU Brugmann ULB, Brussels, Belgium, 2School of Dentistry, University of Athens, Athens, Greece, 3Center for Observational Research, Amgen - USA, Thousand Oaks, CA, USA, 4Clinical Development, Amgen - Austria, Vienna, Austria, 5Center for Observational Research, Amgen - USA, South San Francisco, CA, USA

Background: Physician knowledge surveys have increasingly been requested of drug manufacturers in the post-authorization setting as part of risk minimization plans. Surveys in pharmacovigilance require considerable time and resource, and result in low response rates and questionable representativeness. After EMA consultation, an educational programme was initiated with ecancer to evaluate the potential of online communities in measuring knowledge of drug safety risks. Here, we describe the baseline survey used to measure basic knowledge of osteonecrosis of the jaw (ONJ) risks among prescribers of bone targeting agents (BTAs).

Methods: Clinical experts developed 8 multiple choice questions on BTAs and ONJ risk as described in the summary of product characteristics. BTAs included denosumab, zoledronate, or pamidronate. Invitations were sent out to ecancer and ECOG-ACRIN members.

Results: Among 501 pts, 115 smoked at diagnosis and 60% quit after; 53% had a tobacco related (lung/head and neck) cancer (TRC); 64% were treated curatively; 40% received adjuvant, 28% palliative treatment. 12% were assessed at only the first visit (87%). Most preferred being assessed by their oncologist (88%); less than half preferred being asked by another healthcare provider (44%), on paper (29%) or electronic surveys (15%). When compared to ex/never smokers, current smokers were more agreeable (54%) to being assessed every visit compared to head and neck cancer pts (TRC); 36% vs 20% P < 0.001). Among current smokers, lung cancer pts were more agreeable (54%) to being assessed every visit compared to head and neck cancer pts (aOR = 2.45 95% CI [0.9-6.5] P = 0.06) and non TRCs (aOR = 2.63 [1.0-6.8] P = 0.05). Among all pts who were older (aOR = 1.03 [1.0-1.1]), curative (aOR = 1.92 [1.1-3.2]) and smoked less (aOR = 0.98 per płyk [0.97-0.99]) were more agreeable to assessment at each visit.

Conclusions: Online professional communities offer a pragmatic and efficient approach for recruitment of physicians for knowledge assessments. Basic knowledge of ONJ risks was high overall in this ecancer proof of concept. The strategy can achieve responses representative of today’s physicians who seek information online. These findings may be compared with knowledge among physicians who may not seek information online.

Legal entity responsible for the study: ecancer

Funding: Amgen

Disclosure: J.J. Body: Consultant for Amgen Inc, O. Nicolato-Galitis: Consultant for Amgen J.M. Sprafka, A. Liede: Amgen Inc. Employee, including stock ownership D. Niepel: Amgen GmbH employee, including stock ownership. All authors have declared no conflicts of interest.

Table: 1600P

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Background: Cardiovascular events are an important cause of mortality in patients cured of colorectal cancer and are also potential complications of new therapies for metastatic CRC. The American Heart Association’s “Simple 7” offers a practical public health conceptualization of cardiovascular health. They include healthy behaviours: non-smoking, active physical activity (MVPA > 150 min/w), healthy diet and low body mass index (BMI); and health factors: no hypertension, no diabetes, no hypercholesterolemia. Whereas factors are non-modifiable, behaviours can be changed. Studies have shown that prevalence of ideal cardiovascular health in the US is only 0.1%.

Methods: Patients with a recent diagnosis of CRC who accepted to participate were prospectively evaluated. BMI, blood pressure, glucose and cholesterol were measured at the hospital. Physical activity was objectively evaluated with accelerometers. Adherence to a healthy diet was evaluated through the PREDIMED (adherence to Mediterranean diet) questionnaire. Information about smoking and past cardiovascular disease or risk factors was obtained from the clinical record.

Results: 91 patients were recruited between March 15 and March 17. 36% were metastatic. Age 65 (25-81); 69% male. BMI 26.2 ± 5.6. Waist 95.6 ± 12 cm. mean MVPA 350 ± 248 min/wk, mean sedentarism 3494 ± 1123. 9% had a history of CV disease (ischemic, cerebrovascular, heart failure). 34% were classified as high CV risk. Only one patient showed an ICVH.

Conclusions: The prevalence of ICVH in a population of Spanish CRC patients was 1%. This population was overall compliant with PA recommendations, adhered to a healthy diet and less than 10% smoke in the last year. Hypertension was the most prevalent risk factor. Overweight was the most prevalent unhealthy behaviour. Interventions should be aimed at reducing BMI. Interventions exploring programs with vigorous physical activity and diet modifications in CRC survivors are warranted.

Legal entity responsible for the study: Ana Ruiz-Casado
Funding: None
Disclosure: All authors have declared no conflicts of interest.

Table: 1601P

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1.1% 91% 90.5% 36% 67% 96% 51% 84.3% 66%

1.1602P:

Additive effect of vinca alkaloids as the risk factor for hearing impairments in the childhood cancer survivors

Background: The survival rate of childhood cancer is approaching to over 80%, and survivorship is gathering more attention. The survivors receive chemotherapy, radiotherapy and surgery in their early life stages, and the risk of ototoxicity is increased. We evaluated the degree of risk of the clinical factors causing the ototoxicity, in childhood cancer survivors.

Methods: We established survivorship program for late effects in Yonsei Cancer Center, Seoul, Korea. In all 153 enrolled survivors in the clinic, 103 survivors were invited to evaluate ototoxicity in their bi-annual visits and the clinical risk factors were reviewed retrospectively.

Results: The median age at diagnosis was 6.0 (0-26). Most common diagnosis was leukemia/lymphoma (N = 30, 30%), and brain tumor was the next (N = 29, 29%). Platinum agents were used in 64%, alkylating agents were in 83% and vinca alkaloid was in 78%. Severe hearing impairments defined as over than 60 dB loss were observed in 3% of left ear and 3% of right ears. The proportion of the survivors who had 20 dB loss in any side of ears was 28%. The 69% of abdomen tumor survivors and 56% of brain tumors had any of hearing impairments, but only 28% of leukemia/lymphoma survivors showed hearing loss (P < 0.001). The class of platinum agents use, vinca alkaloids were adverse factors, however, the class of antimetabolites use or antibiotics use were all protective factors for hearing impairments (P < 0.001, <0.001, 0.006, <0.001, respectively). Both use of platinum and vinca alkaloids showed significantly higher risk of hearing impairments compared with use of none or one class of two classes of agents (P = 0.001 for right ear and P < 0.001 for left ear). Young age at diagnosis (<7.5 years old) showed higher risk of hearing loss in abdomen tumor and brain tumor group (P = 0.006 for right, P = 0.051 for left). Total 5000 cGy or more of head and neck region radiation showed increased risk (P = 0.001 for right, P = 0.007 for left). In multivariate analysis, both use of platinum and vinca alkaloids was independent risk factor (O.R. = 8.1, P = 0.004 for right; O.R. = 8.7, P = 0.004 for left).

Conclusions: Hearing impairments were common late effects in childhood cancer survivors, and vinca alkaloids had additive adverse effects on the platinum use for the hearing loss.

Legal entity responsible for the study: Jung Woo Han
Funding: None
Disclosure: All authors have declared no conflicts of interest.

1.1603P:

Development and validation of chewing swallowing inventory (CSI) in head and neck cancer patients

Background: Chewing and swallowing dysfunction are the common problems in head and neck cancer patients. They may interfere patients’ eating and lead to malnutrition. An easily used tool to assess the problems is needed. The purposes of the study were to (1) develop the Chewing Swallowing Inventory (CSI) and (2) examine the psychometric properties of CSI.

Methods: This is an instrument development and testing study. We recruited adult patients with head and neck cancers in the head and neck cancer outpatient clinics in the medical center in northern Taiwan. The items of CSI was developed based our previous research results, clinical observation, literature review and preliminarily validated by experts panel. Psychometric testing includes content validity, internal consistency reliability, construct validity by examining of its factor structures (exploratory factor analysis), theoretical supported correlation and discriminated constructs by groups. Results: The CSI was a 21-item 0 to 4 Likert’s type scaled with 0 representing “no problem/difficulty at all” and 4 representing “having extremely severe difficulty”. We recruited 175 patients. The results showed that (1) CSI has good internal consistency reliability with Cronbach’s α as 0.93. (2) The factor analysis suggest that CSI contains four clear factors which are chewing, swallowing, tongue moving/stirring and taste and saliva changes which explained 70.32% of variances. (3) CSI has good construct supported correlation with nutrition. (4) CSI had good discriminate validity to differentiate patients with different diagnosis, surgical modalities, treatments, and disease stages.

Conclusions: CSI is a simple, easily used, reliable and validated tool to assess patients’ eating difficulties. It will better support health care professionals to detect HNC patients’ eating related chewing and swallowing problems and provide personalized intervention to prevent malnutrition.

Legal entity responsible for the study: National Taiwan University Hospital
Funding: None
Disclosure: All authors have declared no conflicts of interest.

1.1604P:

The Relationship between Oral Supportive Care and Oral Complications in Cancer Patients Receiving Chemotherapy: A Retrospective Study

Background: Oral supportive care for cancer patients received medical insurance coverage in 2012 in Japan. Management includes not only prevention of wound infection and perioperative pneumonia but also treatment of oral complications during chemotherapy and radiotherapy in cancer patients. We conducted a retrospective study to analyze the efficacy of oral supportive care for cancer patients receiving chemotherapy.

Methods: We retrospectively analyzed consecutive 1,142 cases received antinecrosis chemotherapy in our hospital from April 2013 to March 2017. Results: Patients were 633 males and 509 females aged 23-92 years (median 66). Primary sites were lung in 246, esophagus in 153, breast in 137, head and neck in 112, and others in 454. Treatment was chemotherapy in 752, and concurrent chemoradiotherapy in 390. Before beginning chemotherapy, all patients received a dental check and acquired tooth brushing techniques. We compared the oral hygiene status in 752 patients before the beginning of the therapy and at the 1-month check. Rates of improved, stable and regression status were 56.9%, 23.5%, and 19.6%. Regression appeared due to worsening of general condition, and also to oral mucositis among head and neck cancer patients. Oral supportive care was continued to maintain good oral hygiene, detect oral
complications early and manage them with dental treatment, dental extraction, mechanical cleaning, medicine, mouthwash and topical ointment and analgesics. Oral complications of Grade 3 (NCI-CTCAE ver. 3.0) were antiseptic agents-related osteonecrosis of the jaw, teeth infections, and oral mucositis occurred during treatment. There was a significant difference in the incidence of oral complications between more and less than 3 months from the latest dental visit at the start of chemotherapy (p < 0.02).

Conclusions: Oral supportive care for cancer patients receiving chemotherapy should begin before the start of treatment and continue until the successful completion of treatment, especially for the deteriorated patients, head and neck cancer patients, and patients who did not receive dental checkups and cleaning for more than 3 months.

Legal entity responsible for the study: Kobe Minimal Invasive Cancer Center

Funding: None

Disclosure: All authors have declared no conflicts of interest.

605SP  Safety and effectiveness of sensor-controlled scalp cooling in women receiving chemotherapy for primary breast cancer


Gynecologic Oncology, Gynecologic Cancer Center Bonn-Friedenplatz, Bonn, Germany

Background: Sensor-controlled scalp cooling (SCSC) to prevent chemotherapy-induced alopecia (CIA) in patients (pts) with primary breast cancer (PBC) is approved by the FDA. However, SCSC is infrequently used in many countries due to concerns regarding both safety and feasibility. This retrospective analysis sought to obtain more detailed information about the effectiveness and safety of SCSC using the Paxman system (Paxman, Huddersfield, UK) in PBC pts exposed to neoadjuvant (NACT) or adjuvant Ctx (ACT) in the clinical routine.

Methods: 79 pts were identified from our database: NACT, 41 (51.9%); ACT, 38 (48.1%); dose-dense (dd) Ctx, 56 (70.9%); non-dd Ctx 23 (29.1%); premenopausal, 44 (55.7%); postmenopausal, 35 (44.3%). The following Ctx regimens were used: anthracycline-based (A), 1 (1.3%); taxane-based (T), 21 (26.6%); AT-based, 55 (69.6%); non AT-based, 2 (2.5%). Pts were subjected to SCSC during each Ctx cycle. CIA was quantified using the Dean score (DS) determined 3 wks after the last Ctx cycle.

Results: 55 pts (69.6%) completed SCSC with 36 (45.6%) showing complete (DS 0), 15 (19.2%) partial (DS 1-2) control, and 14 (17.9%) partial (DS 3-4). Comparison of CIA incidence between premenopausal and postmenopausal patients showed significant differences (p = 0.006). Among the 55 pts who completed SCSC regimen, 7 (12.7%) pts reported in 4 pts (5.1%) each. Side effects were all not severe and resolved quickly after treatment.

Conclusions: The success rate in our study is in good agreement to previous randomized trials of SCSC in PBC argueing in favor that SCSC is a valuable supportive treatment in the clinical routine.

Legal entity responsible for the study: Onco-nephrology Consortium

Funding: None

Disclosure: All authors have declared no conflicts of interest.

606SP  Pharmacokinetics and safety of FOLFOX therapy in patients undergoing hemodialysis

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Background: Due to a lack of information, there is no guideline regarding the dosage and timing of chemotherapy in cancer patients undergoing hemodialysis (HD).

Therefore, we studied the pharmacokinetics of 5-fluorouracil (5-FU) and oxaliplatin (L-OHP) in cancer patients undergoing HD.

Methods: HD patients (HD group) and patients with normal renal function (control group) who had received either modified FOLFOX4 therapy or modified FOLFOX7 therapy were prospectively enrolled. The blood concentrations of 5-FU and 5-FU metabolites, including 5-fluoro-beta-alanine (FBAL), fluorooctic acid, and ammonia were measured using inductively coupled plasma-mass spectrometry. The blood concentrations of total and ultrafilterable platinum were measured by inductively coupled plasma-mass spectrometry. To estimate the amount of L-OHP removal by dialysis, we also measured the platinum concentration in dialysate.

Results: There were six patients in the HD group and eight patients in the control group. In the HD group, L-OHP was administered just before the HD session in four patients, and on a non-dialysis day in two patients. The amount of L-OHP removal by dialysis was 10% or less of the administered dose, and did not depend on the timing of L-OHP administration. Regarding the 5-FU metabolites, the blood concentration of FBAL was significantly higher in the HD group than in the control group (p < 0.01). We observed hyperammonemia in two patients in the HD group, which was accompanied by elevated blood levels of FBAL and ammonia.

Conclusions: The amount of L-OHP removal by dialysis was up to 10% regardless of the timing of L-OHP administration. Hyperammonemia should be monitored during FOLFOX therapy among HD patients.

Legal entity responsible for the study: Onco-nephrology Consortium

Funding: None

Disclosure: M. Yanagita: Advisory board of Astellas and receives research grants from Astellas, Chugai, Daiichi Sankyo, Fujisaki, Kyowa Hakko Kirin, Mitsubishi Tanabe Pharma Corporation, MSD, Nippon Boehringer Ingelheim, and Torii. All other authors have declared no conflicts of interest.
Health related quality of life (HRQOL) assessment for patients with advanced renal cell carcinoma (mRCC) treated with tyrosine kinase inhibitor (TKI) using electronic patient reported outcome (PRO) in daily clinical practice

Background: mRCC, two therapies are mainly used in first line setting: pazopanib and sunitinib. These two TKI are equally effective in terms of survival however they are responsible for frequent adverse events. Physician mainly use a RECIST progression-free survival (PFS) and NCI CTCAE safety as a guide to evaluate treatment efficiency and tolerance. In contrast HRQOL assessment is often restricted to clinical trial. It could be of particular interest to evaluate HRQOL in daily clinical practice in order to adequately choose and manage therapy. Currently the development of Information and Communication Technology may allow HRQOL monitoring in routine practice. The objective of the QUANARIE Study is to evaluate the feasibility of HRQOL assessment in daily clinical practice for patients with mRCC treated with TKI using electronic PRO.

Trial design: QUANARIE study (NCT03062410) is an interventional, prospective, multicenter trial involving 9 french oncological centers. Patients diagnosed with mRCC initiating TKI anti VEGF treatment (Sunitinib or Pazopanib) will be invited to complete the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 cancer specific questionnaire and the EQ-5D before each visit with the physician. Questionnaires completion will be done by patients on tablets and/or computer terminals via the CHES software (Computer-based Health Evaluation System) at hospital before consultation or at home via secured portal. Physician will immediately have access to a visual summary of HRQOL evaluation. Primary objective is to assess the feasibility of routine assessment of HRQOL evaluation by the rate of filled questionnaires at 12-months. Secondary objectives are: exhaustiveness, acceptability and effectiveness. Physician’s satisfaction with electronic HRQOL evaluation will be assessed. We hypothesized that 80% of filled questionnaires at 12-months would be meaningful. A sample size of 56 patients would be needed. Enrollment is expected to last for 6 mo. Study started in April 2017. Update will be displayed on poster during ESMO congress.

Clinical trial identification: NCT03062410

Legal entity responsible for the study: University Hospital Jean Minjoz

Funding: Novartis

Disclosure: All authors have declared no conflicts of interest.
Background: Cancer cachexia is a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass that cannot be reversed by conventional nutritional support alone. Cachexia has a high prevalence in cancer and a major impact on patient physical function, morbidity and mortality. Despite the consequences of cachexia, there is no licensed treatment and no standard of care. It has been argued that the multifactorial genesis of cachexia lends itself well to therapeutic targeting through a multimodal treatment. Following a successful phase II trial, a phase III trial is underway.

Trial design: MENAC is a multicentre, open, randomized phase III study comparing multimodal intervention and standard cancer care versus standard cancer care alone. Patients treated for incurable lung and pancreatic cancer will be allocated randomly to receive the multimodal intervention, either immediately, or after endpoint at six weeks. The intervention is based on evidence to date and consists of Non-steroidal Anti-inflammatory Drugs (NSAID) and an EPA containing oral nutritional supplement to reduce inflammation, a physical exercise programme consisting of both resistance and aerobic exercises to increase anabolism, as well as dietary counselling aiming to promote energy and protein balance. The overall aim is to reduce weight loss, improve food intake and maintain physical function by establishing basic supportive care for cachexia. From a patient perspective, a short-term effect will be to improve physical and psychological function and reduce symptom burden. Change in body weight is primary endpoint. Secondary endpoints are change in muscle mass (CT technique) and physical activity (ActiPA PAL activity meter). There are several exploratory endpoints. The trial is ongoing and patients are recruited from several sites in Europe and Canada, we aim for 240 patients. If positive, the results will be practice changing for supportive treatment of patients with cancer.

Clinical trial identification: NCT02350926
Legal entity responsible for the study: NTNU through PRC is coordinating the running of the trial.

Funding: The European Union through the European Clinical Research Infrastructures Network (ECRIN) Canadian Institute for Health Research Marie Curie and Raising Tide foundation Norwegian Cancer Union The Omega 3 capsules are received free of charge from Pronova BioPharma Norge AS. The oral nutritional supplements are received free of charge from Abbott Nutrition

Disclosure: All authors have declared no conflicts of interest.

Gastrointestinal Cancers Symposium). However, because this report showed a retrospective data from single institutional small cohort by reviewing medical records, we might have underestimated the incidence of EDs. So, we have conducted this prospective cohort study to confirm the incidence of EDs induced by S-1 more precisely.

Trial design: This is a multicenter prospective cohort study to evaluate the incidence of EDs and ophthalmologic changes in GI cancer patients received S-1 chemotherapy. The key eligibility criteria are as follows: 1) Histologically confirmed carcinomas in GI cancer, including esophageal, gastric, colorectal, pancreatic, and biliary tract cancer; 2) The patient who receives chemotherapy including S-1; 3) No prior medication of S-1; 4) No lachrymal duct obstruction and less than three points of Cancer conjunctiva epithelium disorder score. All participants receive four times of ophthalmological examinations. The primary endpoint is cumulative incidence of epiphora in periods from start of S-1 chemotherapy to 12 weeks after induction S-1. The secondary endpoints are cumulative incidence of epiphora in overall S-1 chemotherapy periods, the time of onset and severity of epiphora, the situation of ophthalmological intervention, ophthalmological changes, risk factors of epiphora, and QOL. Because we supposed that incidence of epiphora at 12 weeks after inducing S-1 is 10% as already reported, we calculated the sample size as 160 based on precision of the 95% confidence interval and aimed to recruit 180 patients considering the possibility of 10% dropouts. This study is supported by Non-Profit Organization Hokkaido Gastrointestinal Cancer Study Group.

Clinical trial identification: UMIN 0000271924 24, June, 2017

Legal entity responsible for the study: Hokkaido Gastrointestinal Cancer Study Group

Funding: None

Disclosure: S. Yuki: Honoria: Taiho Pharmaceutical Y. Sakata: Consultant fee from Taiho Pharmaceutical Co., Ltd., Y. Komatsu: Grants for research and donations: Taiho Pharmaceutical Co., Ltd., All other authors have declared no conflicts of interest.

1613TP Outpatient monitoring with an eTool: self managed or with pro active intervention?
A Phase I safety study of topical Calcitriol (BPM 31543) for the prevention of chemotherapy-induced alopecia (CIA)


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Background: Chemotherapy-induced alopecia (CIA) may lead to significant psychosocial and quality of life issues. Currently there are no FDA approved therapeutic agents available to prevent CIA. In murine studies, topical calcitriol reduced CIA, likely due to arrest of cell cycle in healthy hair follicles and reducing sensitivity of follicular epithelium to chemotherapy.

Trial design: A 3+3 dose-escalation Phase 1 study with 3 to 6 patients at each dose level (5/10/20/40/60/80 μg/mL) to determine the maximum tolerated dose (MTD) and the overall safety and tolerability of a topical compound BPM31543 (Calcitriol) in patients with a diagnosis of breast cancer, gynecologic cancer and sarcomas. Eligible patients receiving a taxane-based chemotherapy regimen applied 1mL of BPM31543 twice daily at each cohort dose level 14 or 7 days prior to initiation of chemotherapy and then continued twice daily for 3 months or until termination of chemotherapy. In order to determine the MTD, dose escalation occurred in stepwise increments of the immediate prior dose group, in the absence of grade 3 or greater toxicities attributed to the topical calcitriol. Dose-limiting toxicity (DLT) was determined during Cycle 1 (i.e., the first 28 days of topical agent application). Patients were managed with adequate safety monitoring and pharmacokinetic (PK) analysis in order to determine levels of exposure. The potential efficacy (secondary objective) of the topical calcitriol was evaluated by photographic assessment using a Canon digital camera system (to ensure standardization and uniformity among all enrolled patients) in addition to patient self-assessments.

Clinical trial identification: NCT01588522

Legal entity responsible for the study: BERG, LLC

Funding: BERG, LLC

Background: Available 2nd line chemotherapies for relapsed malignant pleural mesothelioma (MPM) have limited activity. Results from early clinical trials - including the mesothelioma cohort of the KEYNOTE-082 phase II/III trial - show promising activity of various PD-1 (ligand) checkpoint inhibitors in MPM. Pembrolizumab has been used off-label in Switzerland as 2nd and further line treatment in patients with MPM.

Methods: Cancer centers in Switzerland entered data on patients having received pembrolizumab for MPM into this retrospective registry. Patient characteristics including age, gender, histology, stage at diagnosis and previous treatments were collected. Outcomes of pembrolizumab were assessed by the local investigators using standard RECIST v1.1 criteria. PD-L1 expression was determined centrally. Outcomes of pembrolizumab were assessed by the local investigators using standard RECIST v1.1 criteria. PD-L1 expression was determined centrally.

Results: We collected data on 48 patients (median age 68 years) having received pembrolizumab for relapsed MPM between September 2015 and April 2017. Pembrolizumab was the 2nd line of treatment (after platinum-pemetrexed +/- bevacizumab) in 30 patients (63%). Twenty-eight patients (59%) had an ECOG 0/1 at the beginning of pembrolizumab (as in the KEYNOTE-082 trial). Responses and survival outcomes are listed in Table. Investigator-reported toxicity was as follows: 15 treatment-related adverse events occurred in 14 patients (29%). Five events (10%) were grade 3-4 (2 patients with hepatitis, 1 with heart failure, 1 with non-cardiac chest pain and 1 with nephrotic syndrome). Seven patients (15%) discontinued treatment due to an adverse event.

Conclusions: This is the largest reported cohort of mesothelioma patients treated with pembrolizumab thus far, and the first with any kind of anti-PD(L)1 antibody in a "real-life" setting. Compared to available second- and beyond-line treatment options, response rates and survival outcomes were promising in the unscreened population, while patients with ECOG 0-1 receiving pembrolizumab in 2nd line seemed to benefit substantially. Response rates as well as the incidence of treatment-related adverse events occurred in 14 patients (29%). Five events (10%) were grade 3-4 (2 patients with hepatitis, 1 with heart failure, 1 with non-cardiac chest pain and 1 with nephrotic syndrome). Seven patients (15%) discontinued treatment due to an adverse event.

THEROAC MALIGNANCIES, OTHER

Pembrolizumab as second or further line treatment in relapsed malignant pleural mesothelioma: A Swiss registry

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Background: Available 2nd line chemotherapies for relapsed malignant pleural mesothelioma (MPM) have limited activity. Results from early clinical trials - including the mesothelioma cohort of the KEYNOTE-082 phase II/III trial - show promising activity of various PD-1 (ligand) checkpoint inhibitors in MPM. Pembrolizumab has been used off-label in Switzerland as 2nd and further line treatment in patients with MPM.

Methods: Cancer centers in Switzerland entered data on patients having received pembrolizumab for MPM into this retrospective registry. Patient characteristics including age, gender, histology, stage at diagnosis and previous treatments were collected. Outcomes of pembrolizumab were assessed by the local investigators using standard RECIST v1.1 criteria. PD-L1 expression was determined centrally. Outcomes of pembrolizumab were assessed by the local investigators using standard RECIST v1.1 criteria. PD-L1 expression was determined centrally.

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Conclusions: This is the largest reported cohort of mesothelioma patients treated with pembrolizumab thus far, and the first with any kind of anti-PD(L)1 antibody in a “real-life” setting. Compared to available second- and beyond-line treatment options, response rates and survival outcomes were promising in the unscreened population, while patients with ECOG 0-1 receiving pembrolizumab in 2nd line seemed to benefit substantially. Response rates as well as the incidence of treatment-related adverse events were consistent with the KEYNOTE-028 report. Further results including subgroup analysis by PD-L1 expression will be presented at the meeting.

Legal entity responsible for the study: Department of Oncology, Kantonsspital Graubünden, Chur

Funding: Krebsliga Graubünden, Chur, Switzerland


Y. Metaxas: MSD travel grant.

All other authors have declared no conflicts of interest.

Table: 16150 Outcomes

<table>
<thead>
<tr>
<th>Table 16150 Outcomes</th>
<th>total (n = 48)</th>
<th>ECOG 0-1 (n = 28)</th>
<th>ECOG 0-1 and 2nd line Pembrol (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>25% (81 CR + 11 PR)</td>
<td>32% (1 CR + 8 PR)</td>
<td>42% (1 CR + 7 PR)</td>
</tr>
<tr>
<td>DCR</td>
<td>52% (incl. 13 SD)</td>
<td>57% (incl. 7 SD)</td>
<td>74% (incl. 6 SD)</td>
</tr>
<tr>
<td>mPFS (95% CI), months</td>
<td>3.2 (2.6 - 4.8)</td>
<td>3.7 (2.8 - 6.7)</td>
<td>5.3 (3.6 - NR)</td>
</tr>
<tr>
<td>mOS (95% CI), months</td>
<td>7.9 (6.2 - NR)</td>
<td>9.3 (6.8 - NR)</td>
<td>NR (8.2 - NR)</td>
</tr>
<tr>
<td>alive at 6 months (95% CI)</td>
<td>65% (52 - 81%)</td>
<td>72% (56 - 92%)</td>
<td>77% (59 - 99%)</td>
</tr>
<tr>
<td>alive at 12 months (95% CI)</td>
<td>28% (15 - 53%)</td>
<td>43% (24 - 77%)</td>
<td>52% (29 - 95%)</td>
</tr>
</tbody>
</table>

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Multiplexed targeted proteomics signature for serum diagnostic of malignant pleural mesothelioma

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Did you know that multiplexed targeted proteomics can significantly improve the accuracy of mesothelioma detection in serum? A study led by F. Cerceco and colleagues investigated the use of a multiplexed targeted proteomics signature for the detection of malignant pleural mesothelioma from serum samples. The researchers observed a substantial improvement in the accuracy of mesothelioma detection, with a signature that had an area under the curve (AUC) of 0.76 in discriminating malignant pleural mesothelioma from asbestos exposed donors in a training set of 212 donors.

In conclusion, the multiplexed targeted proteomics signature can improve the accuracy of mesothelioma detection in serum, offering a promising approach for the early detection of this challenging disease.
Malignant pleural mesothelioma immune microenvironment and checkpoint expression before and after systemic cytotoxic treatment


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Background: Tumor immune microenvironment (TME) plays a role in Malignant Pleural Mesothelioma (MPM) pathology and patients outcome. PD1/PDL1 checkpoint inhibitors are currently under investigation as innovative promising treatment of MPM, even though no definitive predictive markers have been defined so far. PDL1 expression and TME are dynamic in tumor samples. The object of this preliminary analysis is a subset of MPM paired samples analyzed before and after induction chemotherapy (ct) in order to assess TME and PDL1 heterogeneity and dynamism over time.

Methods: Inflammatory cells in the intratumoral (IT) and peritumoral (PT) stroma were characterized by immunohistochemistry (IHC) using monoclonal anti-CD20 (B lymphocytes), CD3, CD4 and CD8 (T lymphocytes) and CD68 (macrophages) antibodies, and quantified as percentage in neoplastic area. PDL1 expression in tumor cells (TC) and immune cells (IC) was evaluated by IHC using Ventana SP263 antibody (Roche) and quantified as percentage of expressing cells. Difference between naive and treated samples was assessed through Mann-Whitney test.

Results: 15 paired MPM specimens (14 epithelioid and 1 biphasic) obtained for diagnostic purpose before platinum-pemetrexed ct and at the time of relapse were analyzed. After ct MPM samples showed PT and IT increase of CD68 + macrophages and CD3 + T lymphocytes, even though only peritumoral CD3 + lymphocytes significantly increased (p=0.008). CD4 + and CD8 + lymphocytes were lacking in naive samples, while CD8 + significantly increased after ct (median value PT pre vs. post = 3% vs. 30%, p=0.02; median value IT pre vs. post = 5% vs. 19%, p=0.007). CD3 +/CD68 + ratio increased after ct, even though without statistical significance. No IT B lymphocytes were observed, a small increase at PT level was shown after ct. Ct induced PDL1 expression in tumor cells and even more in lymphomonoctytic infiltrate (median value pre vs. post = 0% vs. 50%, p=0.003).

Conclusions: Ct significantly increases cytotoxic T lymphocytes at PT and IT level in MPM samples and PDL1 expression in IC. These data confirm the strong rationale for the combination of IHC and ct as promising treatment of MPM. Legal entity responsible for the study: Istituto Oncologico Veneto IRCCS

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Outcomes of malignant pleural mesothelioma (MPM) patients (p) treated with immune-oncology drugs (IO) in clinical trials


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Background: The increasing incidence and poor outcome associated with MPM requires identification of effective treatment options. Initial data have demonstrated beneficial effects of IO in MPM, however recent results of clinical studies with immune checkpoint inhibitors (CTI) are not so encouraging. The aim of this study is to evaluate the outcomes of p with MPM treated with immunotherapy in clinical trials at our institution.

Methods: 20 MPM p treated with IO at Vall d’Hebron Institute of Oncology between September 2012 and December 2016 were reviewed. Survival data were calculated by the Kaplan-Meier method. The associations of type of immunotherapy with outcomes were assessed with Cox regression models.

Results: Patient’s characteristics: median age 63 years (45-77 years), males: 62%, performance status (PS) 1.86%, asbestos exposure: 82%, stage III at diagnosis: 51%, epithelial subtype: 82%. All p were treated with chemotherapy, 90% received cisplatin plus pemetrexed as first line with median progression free survival of 9.1 months (95%CI 7.6-10.7). Clinical trial with IO was offered as second-line regimen in 65% and third line in 35%. Target of IO was CTLA4: 60%, PD-1: 25% and other CPI single agent 19% (LAG3, GITR, CD40). Overall, disease control rate at 4 months was 40%. Reasons for treatment receiving from BMS and Roche. M.A. Socin: Honorary and payment for consultation from Genetech and their institution has received funding from Pfizer. U. von Wangenheim, J. Barreucco, N. Morni: Employed by Boehinger Ingelheim. G. Saigagit: Honorary from Eli-Lilly, AstraZeneca, Roche, Pfizer; MSD: payment as consultant from Eli-Lilly; travel expenses by Bayer and has been paid by Eli-Lilly and MSD to participate in a Speaker’s Bureau.

Legal entity responsible for the study: NA

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Abstracts of the 16th Annual Congress of the Spanish Society of Medical Oncology (SEOM) and 18th Spanish Congress of Chemotherapy (CSEC) 2017

Annals of Oncology

Table: 1621P Multivariate Cox Regression Analysis of Overall Survival

<table>
<thead>
<tr>
<th>Histology (non-epithelial vs. epithelial)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage, continuous</td>
<td>1.28 (1.04 - 1.56)</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td>ECOG PS, continuous</td>
<td>1.62 (1.42 - 2.32)</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td>Baseline glycemia, continuous</td>
<td>1.80 (1.08 - 2.98)</td>
<td>0.023</td>
</tr>
</tbody>
</table>

Conclusions: Baseline hyperglycemia was independently associated with shorter survival in this cohort of patients with MPM. Confirmation of its prognostic role in larger cohorts is warranted.

Legal entity responsible for the study: Catalan Institute of Oncology
Background: Malignant pleural mesothelioma (MPM) is the malignancy with poor prognosis. Most patients with MPM present severe symptoms such as pain, dyspnea and fatigue. Because of the symptoms and poor prognosis, MPM survivors would have poor Quality of Life (QOL), however, their QOL has not been well evaluated.

Methods: Subjects were the survivors of MPM. We asked the cancer hospitals in Japan and MPM Patients’ Association to distribute the self-administered questionnaire. QOL was evaluated using scales of the EORTC-QLQ-C30 and QoLoKo short version. In addition to the QLQ-C30, clinical factors were collected using the CoQoLo scale showed MPM survivors had good relationships with their doctors, whereas, they suffered from physical and psychological pain, and had the feeling to be a burden to others. Global health status score evaluated by QLQ-C30 were significantly better among survivors with good PS, >2 years from diagnosis, and female. Similarly, good PS and >2 years from diagnosis were the factors caused higher total score of QoLoKo core domains.

Results: In total, 133 survivors with MPM participated in the study. Regarding the QOL, evaluated by QLQ-C30: functional scales were poor (scores < 50), while symptom scales were not so poor (scores < 50). When stratified by performance status (PS), functional scores were worse in survivors with good PS than those with poor PS, while symptom scales were better in good PS survivors than those with poor PS. CoQoLo scale showed MPM survivors had good relationships with their doctors, whereas, they suffered from physical and psychological pain, and had the feeling to be a burden to others. Global health status score evaluated by QLQ-C30 were significantly better among survivors with good PS, >2 years from diagnosis, and female. Similarly, good PS and >2 years from diagnosis were the factors caused higher total score of QoLoKo core domains.

Conclusions: Survivors with MPM had physical and psychological difficulties. Even the survivors with good PS had functional difficulty. Individualized supports are required for survivors with MPM.

Legal entity responsible for the study: Nobukazu Fujimoto

Disclosure: Ministry of Health, Labour and Welfare, Japan

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1623P Staging and assessment of the response to PET-CT treatment in non-small cell lung carcinoma

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Background: Non-small cell lung cancer (NSCLC) is the leading cause of death from tumors in Western countries. Mediastinal involvement is the most important factor to determine treatment and prognosis. The aim of this study was to analyze the concordance between histological mediastinal staging with that demonstrated by positron emission tomography and computed tomography (PET-CT), in addition to defining the characteristics of this population.

Methods: We prospectively evaluated 244 patients diagnosed with NSCLC at Puerta de Hierro Hospital, from 2009 to 2016. Mediastinal staging was determined by imaging (CT and PET-CT) and anatomo-pathological examination (endobronchial ultrasound, mediastinoscopy or lymphadenectomy). Variables collected included tumor size by CT and PET-CT, lymph node involvement, treatment, and survival. The findings of PET-CT were compared with the histological findings to determine the sensitivity, specificity, and positive (PPV) and negative (NPV) predictive values.

Results: Median of age was 66 years, 74% patients were male,22% were non-smokers. Most common histologies were adenocarcinoma (49%) and squamous (37%). 12% patients presented EGFR mutations (4% wild type and 3% were ALK translocated. Staging results by PET-CT were: I (26%), II (21%), III (26% in B and 14%) and IV (10%). The correlation in staging between CT and PET-CT, obtaining a kappa index of 0.9 (p < 0.0001) (Landis and Koch: almost perfect agreement). In stages I and II the correlation between PET-CT and final outcome after surgery was 61.

1624P Liquid Withdraw technique prominently reduced the incidence of pneumothorax and improved tumor tissue amount of CT-guided cutting needle lung biopsy: A retrospective study

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Background: CT-guided cutting needle-lung biopsy is important for the diagnosis of lung cancer. In the area of precision medicine, it has become important to obtain adequate tumor tissue for the molecular testing. Pneumothorax is one of the most prevalent complications of the biopsy. In previous study, we found that “liquid withdraw” technique (to inject small amount of liquid during the withdrawal of the needle) can prominently reduce the incidence of pneumothorax. In this report, we retrospectively studied 92 CT-guided lung biopsy to investigate the role of this technique in reducing complications and improving biopsy effectiveness.

Methods: From Jan 1st, 2014 to Nov 30th, 2016, we retrospectively studied 92 CT-guided lung biopsy using liquid withdraw techniques in 90 patients. The pathologies (cytology, histology and EGFR mutation status) and complications secondary to biopsy procedure (pneumothorax, bleeding, etc.) were noted. Pneumothorax and bleeding was graded as mild (mild and very mild), moderate, and severe.

Results: 88 cases were diagnosed out of 92 biopsies (95.7%), of which 60 cases were adenocarcinoma. Among 52 cases of adenocarcinoma who consented EGFR mutation test, only 1 case (1.9%) was failed due to insufficient tissue. Among all the biopsies, when cutting tumor tissue 4-6 times per procedure, the incidence of pneumothorax happened. No severe pneumothorax occurred. No other severe complications happened.

Conclusions: Compared to lung biopsy without liquid withdraw, the incidence of pneumothorax using “liquid withdraw technique” was reduced from approximately 35% to 19.6% (14.1% were very mild pneumothorax and 4% were severe pneumothorax). The liquid withdraw technique also resulted in low rate of other complications and adequate tissue for diagnosis and treatment planning of lung cancer. Next, we are planning to conduct a prospective study to further evaluate the role of liquid withdraw technique in the precision diagnosis and treatment of lung cancer.

Legal entity responsible for the study: The Comprehensive Cancer Center of Drum-Tower Hospital, Medical School of Nanjing University

Disclosure: All authors have declared no conflicts of interest.
Methods: In this Ph II study performed at three cancer centers in Tokyo, we aimed to enroll 26 TC patients previously treated with platinum-based chemotherapy. The patients received 5-1 orally twice daily at a dose of 40-60 mg/m² for 4 weeks, followed by 2 weeks off until progressive disease or unacceptable toxicities. S-1 was used off-label. The primary end point was determining the objective response rate, and secondary endpoints were progression-free survival (PFS), overall survival (OS), and toxicities.

Results: Twenty-six patients (18 males) were recruited between November 2013 and May 2016. The median age was 65 (27-74) years. Among the 26 patients, 23 had squamous cell carcinoma histology and 10 had an ECOG performance status of 0. Additionally, one patient showed complete response and seven patients showed partial responses, resulting in a 30.8% response rate (99% confidence interval [CI], 16.5–50.0) and a 65.4% disease control rate (95% CI, 46.2–80.6). After a median follow-up of 13.4 months, the median PFS was 4.3 months (95% CI, 2.3–7.6 months) and median OS was 23.4 months (95% CI, 12.8–not reached). Treatment-related adverse events (AEs) of grade ≥3 included neutropenia (12%), skin rash (8%), elevated ALT, decreased WBC count, and fatigue (4%). No treatment-related death was observed. However, treatment was discontinued in three patients (12%) because of AEs.

Conclusions: S-1 as a palliative-intent chemotherapy and a cytotoxic agent for refractory TC confirmed clinical activity with good tolerability.

Clinical trial identification: UMIN000010736

Legal entity responsible for the study: National Cancer Center Hospital/The Cancer Institute Hospital of Japan Foundation for Cancer Research/Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital

Funding: None

Disclosure: Y. Goto, S. Kanda, H. Horinouchi, H. Nokihara, N. Yamamoto, M. Nishio, Y. Ohe: Consulting or Advisory Role from Taiho Pharmaceutical All other authors have declared no conflicts of interest.

1626P

Detects esophageal squamous cell carcinoma via liquid biopsy of circulating exosomes

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Background: As with many cancers, survival rates for esophageal squamous cell carcinoma (ESCC) are poor when the disease is diagnosed at a later stage without any symptoms. Exosomes are 40-150nm small vesicles in blood and other body fluids and have been described as promoters of tumor progression. Although the secretory mechanisms of tumour-associated exosomes are still unclear, the use of circulating exosomes as potential non-invasive biomarkers might become promising. The object of this study was to determine what the circulating exosomes from ESCC patients can serve as biomarkers in ESCC.

Methods: Serum samples were obtained from 100 patients with ESCC and 100 healthy volunteers. Exosomes were extracted from Total Exosome Isolation Reagent, and purified by selectively capture tumor-associated epithelial cell adhesion molecule (EpCAM) positive exosomes by magnetic-bead technique. ELISA was performed to measure the expression of CD9 protein. Cell invasion was measured using transwell chamber. Expression levels were compared by using the Mann-Whitney U test, Friedman or Wilcoxon test. Receiver-operating characteristics (ROC) curve was established to evaluate the diagnostic value of exosome for the differentiation between ESCC patients and controls. Univariate analysis of OS and DFS was performed by Kaplan-Meier test.

Results: Expression levels of exosomal CD9 were significantly higher in ESCC patients than in healthy individuals (p < 0.05). The expression levels of exosomal CD9 in different TNM stages and grades were significantly higher than in the controls (p < 0.05, respectively). ROC analysis demonstrated that expression levels of exosomal CD9 distinguished patients with ESCC from healthy individuals with 76% sensitivity and 84% specificity. Kaplan-Meier analysis demonstrated that increased expression of exosomal CD9 was associated with poor OS and PFS in ESCC patients (P < 0.05). In addition, the experiments of delayed processing, freezing and thawing did not affect the expression levels of exosomal CD9. To prevent and wound scratching assay showed that the exosomes could promote cell invasion and migration.

Conclusions: Serum exosomal CD9 might represent potential diagnostic and prognostic biomarkers in ESCC in the future.

Legal entity responsible for the study: Zhejiang Cancer Hospital

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1627TIP

ONCOS-102 and pemetrexed/cisplatin in patients with unresectable malignant pleural mesothelioma

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Background: Mesothelioma is a rare cancer with poor prognosis and limited treatment options, including surgery, radiotherapy and chemo (pemetrexed + cisplatin/carboplatin). Adenoviruses are excellent immunotherapeutic agents with a unique ability to prime and boost immune responses. ONCOS-102 is a granulocyte-macrophage colony stimulating factor (GM-CSF) – expressing oncolytic adenovirus (Ad5/D24-GMCSF). In a prior phase I study of 12 patients (pts) with advanced solid tumors, 40% had stable disease (SD) at 3 months, 11/12 pts had infiltration of CD8+ lymphocytes in lesions, and 10/12 had intraluminal PD-L1 expression increase. Lymphonal immune activation was seen in two pts with mesothelioma.

Trial design: A randomized Phase II study (n = 24) with a non-randomized Phase Ib safety lead-in cohort (n = 6). The study will compare ONCOS-102 and chemo with chemo alone (control arm). Eligible pts have histologically confirmed unresectable disease and are not candidates for curative surgery. Pts can be naïve to chemo, or have received and responded to chemo, but relapsed after at least 6 months thus eligible for renewed chemo treatment. Pts must have measurable disease with tumour accessible to intratumoral injections of ONCOS-102 and biopsies. A Data Safety Monitoring Committee will review data when the first 3 and all 6 pts have completed the Day 64 visit (i.e. after 2 cycles of chemo and 4 injections of ONCOS-102). If safety is acceptable, phase II will start with 10 pts in the control arm, and 14 pts in the experimental arm. Primary objective: Safety. Secondary objectives: 1) Tumour specific immunological activation in peripheral blood and biopsies 2) Response Rate 3) Progression Free Survival 4) Overall Survival and 5) Correlation between immune activation and clinical outcome. Treatment: Single cyclophosphamide dose followed by intratumoral injection of ONCOS-102 at 3x10¹¹ viral particles (VPs) on days 1, 4, 8, 36, 78 and 120. Pemetrexed (500mg/m²)/cisplatin(75mg/m²) is given on day 22 and every 3 weeks for a maximum of 6 cycles. Imaging at baseline, Day 64 and 148. Tumor biopsies from both injected and non-injected lesions at baseline and Day 36.

Clinical trial identification: Eudra CT: 2015-005143-13 ClinicalTrials.gov. NCT02879669

Legal entity responsible for the study: Targovax OY, Helsinki, Finland

Funding: Targovax OY, Helsinki, Finland

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Development of the Manchester Cancer Research Centre Molecular Tumour Board for matching patients to clinical trials based on tumour and ctDNA genetic profiling.

Methods: Patients referred to the Experimental Cancer Medicine Team were consented on clinically relevant matched therapies. We describe our experience of setting up a MTB to deliver a world-class genomic driven oncology programme.

Results: From Apr 2015 to Nov 2016 we recruited 100 patients to Part A. Main tumour types were colorectal (24%), breast (20%) and lung (18%). In 41% of patients a potentially actionable alteration was identified. The main changes were i) optimisation of a bioinformatic pipeline for ctDNA, ii) linking clinical data with genomic data in a single portal, iii) interpretation of unknown variants and iv) linking results to available clinical trials in UK/Europe.

Conclusions: We have successfully implemented a comprehensive molecular profiling programme. The bioinformatic pipeline for ctDNA has evolved through real-life data collection and comparison with tumour/gemini DNA. We are developing a web-based interface for linking clinical and genomic data for visualisation and annotation within the MTB. Variant interpretation software packages are being evaluated for data curation and ability to link with matched clinical trials. Recruitment of 409 patients to Part A of TARGET was underway to match patients with early phase and clinical trials in UK/Europe.

Legal entity responsible for the study: Study sponsor is The Christie NHS Foundation Trust.


Patient experience: From the patient perspective.

Conclusions: Patient experience highlights the potential of targeted therapy and the importance of multi-disciplinary approaches in the clinic and research setting.

Legal entity responsible for the study: Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK.

Disclosure: All authors have declared no conflicts of interest.

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A systematic rapid autopsy program tracks temporal and spatial heterogeneity of human tumors and identifies mechanisms of resistance to targeted therapies.

Methods: Correlation of PD-L1 expression with that of MET, ALK, PTEN proteins by IHC (MET +, ALK +, PTEN −) and mutations in KRAS, EGFR, PIK3CA or MET genes was explored in the large international ETOP Lungcoscope cohort of resected, stages I–III, NSCLC. The DAKO 28-8 immunohistochemistry assay was used to assess PD-L1 expression, and gene mutations testing was based on Fluidigm technology, a microfluidics-based multiplex PCR platform. PD-L1 expression was defined with alternative cut-offs (≥1%, 5%, 10%) for neo- and plasma cell membrane staining.

Results: PD-L1 expression was assessed in 2182 pts, from 15 centers, 51/4277/7 adenocarcinomas (AC)/squamous cell carcinoma (SCC)/other, 49/29/222-stage I/IIb/III, 32/ 54/111 current/former/never smokers, 4% unknown smoking status. For the 1% cut-off, a significant association was detected between PD-L1 and MET expression both for AC and SCC. (PD-L1 positivity in AC: 63% in MET + vs 33% in MET −, p < 0.001; SCC 57% vs 42%, p = 0.005). PD-L1 positivity was more frequent in PTEN expressing AC (48% vs 37% in PTEN loss subgroup, p = 0.0017), but not in SCC (p = 0.62). The association of ALK expression and PD-L1, explored only in the AC, was not significant (p = 0.42). Significant associations were also detected in AC between PD-L1 and ERAS

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and EGFR genes. PD-L1 positivity was higher in KRAS mutated pts (AC: 46% vs 38% in KRAS wild-type (wt), p = 0.022; SCC: p = 0.88), and less frequent in EGFR mutated pts (AC: 27% vs 42% in EGFR wt, p = 0.012; SCC: only 8 mutated pts, no inference can be drawn). No significant correlation was detected between PD-L1 and PIK3CA or MET mutations. Results were analogous for the 5% and 50% cut-offs, with the exception of non-significant association between PD-L1 and EGFR in AC.

Conclusions: In this large NSCLC cohort, PD-L1 positivity (with 1%, 5% or 50% cut-offs) is found to be significantly associated with IHC MET overexpression, expression of PTEN and KRAS mutation.

Legal entity responsible for the study: European Thoracic Oncology Platform (ETOP)

Funding: Bristol-Myers Squibb International Corporation

Disclosure: K.M. Kerr: Consulting or advisory role and paid participation in a speaker’s bureau; Astra Zeneca, BMS, Boehringer Ingelheim, Eli Lilly, Merck KGaA, MSD, Novartis, Pfizer, Roche. L. Bubendorf: Member of advisory boards: BI, MSD, Roche K. Monkhorst; Member of 4 advisory boards: Pfizer, Roche, MSD. All other authors have declared no conflicts of interest.

1633PD

Prominent immune suppressive tumor microenvironment in female never-smoker lung cancer patients with EGFR mutations


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Background: According to genetic and genomic analysis as well as previous clinical research, lung cancer in never-smokers might have pathogenesis and progression different from that of lung cancer among smokers. There has been indirect evidence that different types of mutations in tumors might be related to the altered immune functions.

Methods: Tissues from 110 female patients with lung adenocarcinoma (never-smokers: 102 & smokers: 8) at the Samsung Medical Center, were analyzed by next-generation genomic sequencing including whole-exome seq and RNA-seq. Somatic mutations and gene expression levels of immune signature genes were profiled. The significance for clinical outcome of the selected genes was plotted using Kaplan-Meier method and log-rank test.

Results: Expression biomarkers of immune suppressive cells such as mast cells, macrophage and Treg were prominent in female never-smokers compared to female smokers of lung adenocarcinoma. The data suggest that cells of cytotoxic functions are deactivated in smokers, whereas cells of immune suppressive functions are activated in never-smokers. Specifically as expression of immune markers specific for B-cells, dendritic cells, mast cells and Treg was especially up-regulated (<0.05) in tumors from patients with EGFR mutation (42%), its mutation status may play an important role in augmenting the immune suppressive activity. EGFR mutation positive adenocarcinoma was significantly associated with low level of expression of an immune checkpoint molecule, programmed death ligand 1 (PD-L1), in contrast with high level of cytotoxic T-lymphocyte antigen 4 (CTLA-4) in female never-smokers.

Conclusions: This overall immune suppression in lung adenocarcinoma patients with EGFR mutation might explain the lower response rate of anti-PD-1/PD-L1 blockade to the female never-smokers, which suggests that other approaches to block the immune suppressive microenvironment would be necessary.

Legal entity responsible for the study: The Institutional Review Board of Samsung Medical Center

Funding: Samsung Cancer Research Institute

Disclosure: All authors have declared no conflicts of interest.

1632PD

A novel radiomic based imaging tool to monitor lymphocyte infiltration and outcome of patients treated by anti-PD-1/PD-L1


Radiation Therapy, Radiomics INSERM U100, Institut Gustave Roussy, Villejuif, France; Radiomics INSERM U100, Institut Gustave Roussy, Villejuif, France; Nuclear Medicine, Institut Gustave Roussy, Villejuif, France; Drug Development Department (DIETP), Institut Gustave Roussy, Villejuif, France; INSERM U1170, Gustave Roussy Cancer Campus Grand Paris, Villejuif, France; Radiology, Institut Gustave Roussy, Villejuif, France; Drug Development Department (DIETP), Gustave Roussy Cancer Campus, Villejuif, France; Head and Neck, Gustave Roussy, Villejuif, France

Background: Tumor infiltrating lymphocytes (TILs) appears necessary to trigger anti-cancer activity of anti-PD-1/PD-L1. Radiomics consists in the analysis of quantitative data extracted from standard medical imaging to generate imaging biomarkers. We developed a radiomics-based predictor of TIL and investigated whether such signature could predict the outcome of patients treated by anti-PD1/PD-L1.

Methods: We first developed a predictive model of tumor infiltrating CD8 T cells with RNA-Seq and raw imaging data (CT–Scan) using random forest in 69 HNSCC patients from the TCGA (The Cancer Genome Atlas)/TCIA (The Cancer Imaging Archive) database. CD8 T cells were estimated by the Micronenvironment Cell Populations-counter signature. To validate our tool, this signature was applied to a first independent cohort of 100 patients for which the pathologic TIL was assumed as either high (lymphoma, melanoma, lung, bladder, renal and MSI + cancers; 30 patients) or low (adenocytic ependymoma, low-grade gliomas, uterine sarcoma; 70 patients). Finally, we applied our signature on a second cohort of 139 patients prospectively enrolled in anti-PD-1/PD-L1 phase 1 trials to infer its relation with patient outcome (Overall Survival).

Results: We developed a CD8 radiomics-based signature with six out of the 8 extracted features from CT-scans. As an internal validation, the correlation of this signature with the estimated TCGA CD8 was: spearman’s rho = 0.81 (P < 0.05). In the first external cohort this signature was associated with the assumed lymphocytosis (Wilcoxon test, P < 0.001). When validating our signature in the second external cohort, the median of the CD8 signature predicted score was used to separate patients into two groups. Patients with high predicted CD8 score had significantly better OS (HR = 0.55, 95%CI:0.36–0.86, P = 0.009) and the CD8 signature remained significant after multivariate analysis including BMI score and the number of previous lines of treatment (HR = 0.48, 95%CI:0.29–0.76).

Conclusions: The radiomics-based signature of TIL was validated in two external cohorts. It appears a promising tool to estimate TIL and to infer the outcome of metastatic patients treated with anti-PD-1/PD-L1.

Legal entity responsible for the study: Ferti Charles

Funding: None

Disclosure: L. Verlingue: consulting Adaptapherapy J-C. Soria: Consultancy fees from AstaZeneca, Astex, Clovis, GSK, Gammablats, Lilly, MSD, Mission Therapeutics, Merus, Pfizer, Pharmamar Pierre Fabre, Roche-Genentech, Sanofi, Servier, Symphogen, Takeda. All other authors have declared no conflicts of interest.

1633PD

Co-amplification of KIT/KDR/PDGFR in over 100,000 advanced cancer exomes


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Background: The 4q12 amplicon (4q12amp) which harbors the tyrosine kinases KIT, KDR and PDGFR has been thought to occur as frequently as 3.7% in lung adenocarcinoma (LA) (Ramos et al, 2009) and 5-15% in glioblastoma (GBM) (Holtkamp, 2006; Sterle, 2012) as assessed by a variety of techniques. As 4q12amp is hypothesized to be an oncogenic driver, it remains unclear whether all three kinases participate equally in oncogenesis, or if one kinase can be preferentially targeted by a tyrosine kinase inhibitor (TKI) for patient benefit. We undertook a large-scale genomic analysis to describe the frequency of 4q12 across solid tumors.

Methods: We prospectively analyzed 114,200 primarily advanced stage solid tumors in the course of clinical care using hybrid-capture based comprehensive genomic profiling (CGP) of 186 to 315 genes plus introns from 14 to 28 genes commonly rearranged in cancer.

Results: 4q12amp was present in 0.65% of all cases (740/114,200), with a median copy number of 10, and was most abundant in the following cancers: 4.8% of GBM (155/3,222), 0.83% of lung cancers (191/22,857, 23% approximately being LA), 1.9% of sarco (106/5,391), and 0.77% of breast cancers (92/11,980). Of sarcoma, 7.1% of osteosarcoma (26/367) and 2.82% of soft tissue sarcomas (93/3370) harbored 4q12amp. Of 4q12amp lung cancer cases, the supramajority (96%) did not harbor known oncogenic drivers of NSCLC (alterations of EGF/HER2/MET, ALK/ROS/RET fusions, or BRAF V600E). Index cases of durable responses to pazopanib and imatinib will be described in undifferentiated sarcoma, synovial sarcoma, and head and neck salivary cancers.

Conclusions: 4q12amp is significantly less frequent in GBM and lung cancer than previously reported by non-sequencing techniques, but it is enriched in osteosarcoma and undifferentiated sarcomas. The driver status of 4q12amp is supported both by the predominant mutual exclusivity with other known drivers in lung cancer, and responses to various multi-TKIs. The specificities of the latter may help shed insight into whether singly or multiply targeting KIT/KDR/PDGFR is a pertinent approach for patient benefit.

Legal entity responsible for the study: Foundation Medicine

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Disclosure: U. Disel: Research agreement with Foundation Medicine, which provided funding to run a small number of genomic profiling assay (<15). R. Madison, J. Chung, A. Ortan, A. Benson, J. Webster, P.J. Stephens, A.B. Schrock, V.A. Miller: an employee of and has equity interest in Foundation Medicine Inc. M. Gounder: No COI for this specific work. Advisory board or compensations: Tracena, Dacixa, Karyopharm, Epizyme, Agena S.J. Klempner: Honoraria – Foundation Medicine, Inc. Consulting/Advisory Board – Lilly Oncology, Boston Biomedical S-H.I. Ouf: Stock ownership. Yen Membership of an advisory board or board of directors: Genentech/Roche, Ariad, Pfizer, Novartis, Astra Zeneca Corporate sponsored research S. Ganesan: COI: Merck: Spouse is employee and owns equity Inspira Inc.; am on SAR, own equity and has NVP Novaric consultant J. Ross: Employee of and has equity interest in Foundation Medicine Inc. paid speaker for several pharmaceutical companies. has equity interest in Syper Inc. 5. All: Employee of and have equity interest in Foundation Medicine. I own ~5000 USD in stock and equity and ex-employee. All other authors have declared no conflicts of interest.

Methods: Prospective generation of a collection of pt samples with molecularly-selected FGFRalt tumors [amplified/amp/mRNA high expression/mRNAh/mutated/mut/translocated/trlans(ants)]. We developed a protocol to obtain serial biopsies (bx) during therapy on patient, including ctDNA autopsies, for patient-derived xenografts (PDXs) generation. We collected plasma for analysis of circulating tumor DNA (ctDNA). Clinical benefit (ClinBen) was defined as any tumor shrinkage or disease control for 4 months.

Results: From 2014 to 2017, 40 FGFRalt pt were included [FGFRamp (20)/mRNAh (7)/mut (17)/trans (3)]. 30 cases received an FGFRinh (multi-tyrosin kinase (7), selective reversible (8) or irreversible-FGFR1-inh (14) or FGFR4inh (1)). 8 cases achieved ClinBen (5 breast - 2 FGFRamp, 2 FGFRmut, 1 11q + FGFRamp/1 biliary tract FGFR2trans/1 head/mcG FR/mRNAaim/1 mulicentric carcinomac an FRFRmut). PDX/cbs after progression to FGFRinh (10) and warm autopsies of responding pt (2) will serve to study tumor heterogeneity and resistance mechanisms using novel high-throughput technologies. All PDXs (16 growing/14 in observation) will help in identifying potential predictive biomarkers and further characterizing the mechanism of action of FGFRinh in vivo. In vitro functional profiling of oncogenic activity of FGFRmut (17) will be performed. Blood samples will serve for developing in-house ctDNA analysis to monitor genomic evolution of these 40 pt.

Conclusions: We have successfully developed a powerful precision medicine framework for linking the molecular biology with the best tumor models in parallel with early clinical research. By integrating the knowledge obtained from the analysis of relevant samples, we aim to validate future hypothesis-driven therapies for selected FGFRalt pt and guide the successful development of FGFRinh.

Co-funded by ISCHR-FEDER (PI/10/06)

Legal entity responsible for the study: Vall d'Hebron Institute of Oncology

Funding: ISCIII-FEDER

Disclosure: C. Hierro: Research fundings from Bayer A. Vivancos: Member of advisory boards for AstaZeneca, Symyx, Merck. J. Tabernero: Member of advisory boards for Amsden, Bayer, Boehringer, Celgene, Chugia, Lilly MSD, Merck Serono, Novartis, Pfizer, Roche, Sanofi, Symphogen, Taiso and Takada V. Serra: Research fundings from Bayer HealthCare J. Rodon: Member of advisory boards for Novartis, Lilly, Orion and has received research fundings from Principa and Bayer All other authors have declared no conflicts of interest.

Methods: EPHA2 receptor is involved in vivo acquired resistance to anti-Epidermal Growth Factor Receptor (EGFR) treatment in metastatic colorectal cancer (mCRC)

Background: EPHA2 tyrosine kinase receptor is implicated in cell growth, migration, and invasiveness in a wide range of cancers. We studied its role as a potential marker of resistance to anti-EGFR drugs in colorectal cancer (CRC). We previously demonstrated that EPHA2 was differently activated among a panel of CRC cell lines with primary and acquired resistance to cetuximab and the use of ALW-IV-41-27 (a selective FGFR inhibitor) in combination with cetuximab was able to revert this resistance in in vitro experiments (abstract presented at 2016 ESMO Congress in Copenhagen). Here we present the study on in vivo models.

Methods: EGF-dependent SW48 and LM1215 cell lines were engrafted into nude mice and treated with cetuximab until disease progression. Once tumors became resistant (SW48-CR and LM1215-CR) mice were randomized in groups of 10 mice each and assigned to receive ALW-IV-41-27 as single agent or in combination with cetuximab, no treatment and cetuximab alone group served as control. ALW-IV-41-27 was administered daily at 30 mg/kg by oral gavage and cetuximab intraperitoneally at 1 mg/kg two days a week. Treatment was performed for three weeks, then mice were euthanized and protein expression in tumors was analysed by Western Blot.

Results: The combination of the two drugs induced a significant reduction of tumor volume since the first administration. A reduction of 50% of tumor volume was found in 5 out 10 LM1215-CR mice treated with ALW-IV-41-27 as single agent. This effect was maintained after cessation of therapy and induced prolonged survival. Tumor protein analysis by WB demonstrated a strong reduction of EPHA2 expression and activation in mice treated with the combination of ALW-IV-41-27 and cetuximab, accompanied by a significantly inhibition of activated pMAPK and pAKT.

Conclusions: These results highlight the role of EPHA2 as a potential therapeutic target in mCRC treatment.

Legal entity responsible for the study: Università della Campania Luigi Vanvitelli

Funding: None

Disclosure: All authors have declared no conflicts of interest.
**1637P**

**Eph A2 expression is a predictive biomarker of poorer activity and efficacy of FOLFR1 + cetuximab in mCRC WT metastatic colorectal cancer (mCRC) patients (pts) in the CAPRI GOI trial**

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**Background**

Eph A2 promotes tumor growth, invasiveness and angiogenesis in mCRC. Targeting Eph A2 could overcome resistance to anti-epithelial growth factor receptor inhibitors in colon cancer preclinical models.

**Methods**

Formalin-fixed paraffin-embedded tumor specimens from 82 mCRC pts treated with cetuximab + FOLFR1 as first line therapy in the CAPRI GOI trial were assessed for Eph A2 expression by immunohistochemistry. Eph A2 levels were evaluated developing an HSCORE [1 x (% cells 1+) + 2 x (% cells 2+) + 3 x (% cells 3+)] (range 0-300). A cut-off was set by ROC analysis to define high (>30) and low (£30) Eph A2 levels.

**Results**

Eph A2 expression was found in 53/82 (66%) cases. According to HSCORE Eph A2 levels were low in 54 (66%) and high in 28 (34%) samples. Eph A2 expression resulted in mostly complete membranous staining. Tumor stroma was positive in 15/82 (18%) cases. In most of these cases an intense immune infiltrate was observed. Non-tumor adjacent normal mucosa was assessable in 34/82 samples. Eph A2 was expressed in 12/15 (80%) more frequently in dysplastic epithelial areas. A significant correlation between Eph A2 expression in tumor and stroma was found (p < 0.001). Eph A2 was more frequently expressed in less differentiated tumors (p = 0.02), as well as in left- and right-sided tumors (17/28 (61%), 11/28 (39%), respectively p = 0.04). Eph A2 expression was associated with higher rate of disease progression (PD) 8/28 (29%) vs 5/54 (9%) (p = 0.02), and with worse median PFS (18.6 m (CI95% 6.4-10.8) vs 12.3 m (CI95% 10.4-14.2) p = 0.005), both in left and right-sided tumours. Moreover, median OS was 28.4 m (CI95% 13.1-43.7) vs 39.8 m (CI95% 32.0-49.4), although this result did not reach statistical significance (p = 0.23).

**Conclusions**

Eph A2 levels were significantly associated with a worse PFS and an increase in PD in mCRC pts with cetuximab + FOLFR1 as first line therapy in the CAPRI GOI trial, in both right- and left-sided tumors. A similar trend was observed for OS. Eph A2 might represent an additional predictive biomarker of lack of efficacy in mCRC pts treated with cetuximab + FOLFR1.

**Legal entity responsible for the study:** Department of Clinical and Experimental Medicine “F. Magrassi” Università degli studi della Campania “Luigi Vanvitelli”, Naples, Italy.

**Funding:** AIRC

**Disclosure:** F. Ciardiello: Advisory boards: Merck Serono, Lilly, Roche, Bayer, Amgen, Pfizer. E. Martinelli: Advisory boards: Merck Serono, Amgen. All other authors have declared no conflicts of interest.

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**1638P**

**Clinical value of cfDNA and CTCs in EGFR mutations detected in advanced NSCLC**

S. Calabuig Fariñas1, E. Jantus-Leventer1, A. Fernández1, C. Mayo de las Casas1, A. Blasco2, C. Aguilar3, N. Jordana4, A. Balada4, M. Garzón5, M. Pérez6, S. Calabuig Fariñas1

1Laboratorio de Oncología Molecular, Fundación para la Investigación, Hospital General Universitario de Valencia-CIBERONC, Departamento de Patología, Universitat de València, Valencia, Spain; 2Laboratorio de Oncología Molecular, Fundación para la Investigación, Hospital General Universitario de Valencia-CIBERONC, Departamento de Biotecnología, Universitat Politècnica de València, Valencia, Spain; 3Servicio de Oncología Médica, Hospital General Universitario de Valencia-CIBERONC, Valencia, Spain; 4Laboratorio de Oncología Médica, Universidad de Valencia-CIBERONC, Valencia, Spain; 5Servicio de Oncología Médica, Hospital General Universitario de Valencia-CIBERONC, Valencia, Spain; 6Servicio de Oncología Médica, Fundación para la Investigación, Hospital General Universitario de Valencia-CIBERONC, Valencia, Spain; 7Servicio de Oncología Médica, Hospital General Universitario de Valencia-CIBERONC, Servicio de Oncología Médica, Hospital General Universitario de Valencia-CIBERONC, Departamento de Medicina, Universitat de València, Valencia, Spain

**Background**

Targeted inhibition of EGFR represents a milestone in lung cancer treatment. Development of sensitive and accurate techniques allows the detection of EGFR mutations in liquid biopsies. CTCs and cfDNA analysis may be useful in treatment selection, response monitoring, and early resistance detection. The aim of this study was to correlate the EGFR mutational status of CTCs and cfDNA at diagnosis and during follow-up in non-small-cell lung cancer (NSCLC) patients.

**Methods**

The study included 22 EGFR mutated NSCLC patients, blood samples were collected and repeated sampling was performed during follow-up and at progression. cfDNA was obtained from plasma, whereas CTCs were isolated by size using a filtration-based device (ScreenCell), characterized and enumerated by H&E. CTC and cfDNA genotyping was performed by PNA-Taqman assay for EGFR 19del, L858R, G719X and T790M detection.

**Results**

Patient’s median age was 65 years, 81.8% were female, 70% never-smokers and 94% were ADC. The follow-up ranged from 3 to 48 months. Out of the 22 EGFR mutated tumors identified, 12 harbored exon 19 deletion, 7 L858R mutation in exon 21, 2 T790M mutation and one presented exon 19 deletion and T790M together at diagnosis. All patients were treated with EGFR-TKIs. 110 blood samples were evaluated at baseline and during follow-up. CTCs were observed by H&E with a range 1-30/3 ml. Our results confirm that detected mutations can provide early outcome information. Early undetectable blood mutations after EGFR-TKI might predict a large clinical response, whereas in TKI-resisters patients, EGFR mutation remained undetectable, its reappearance preceded disease progression. In case of persistent mutation during treatment, a rapid progression and excess was observed. A baseline T790M mutation in EGFR TKI-naive patient has been reported with rapid progression and excess.

**Conclusions**

Results suggest that analyses of EGFR mutations in CTC and cfDNA have important clinical implications and can be a useful biomarker of diagnoses, response to therapy and early detection of mechanisms of TKIs resistance, in advance of clinically detectable disease. This work was supported by Astra Zeneca (ISSRES0110), the RD12/0036/0025 ISCIII, grants from the FEDER and López-Trigo Grant.

**Legal entity responsible for the study:** Fundación para la Investigación del Hospital General Universitario de Valencia

**Funding:** This work was supported by Astra Zeneca (ISSRES0110), the RD12/0036/0025 ISCIII, grants from the Fondo Europeo de Desarrollo Regional (FEDER) and López-Trigo Grant.

**Disclosure:** All authors have declared no conflicts of interest.

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**1638P**

**Tucatinib, a HER2 selective kinase inhibitor, is active in patient derived xenograft (PDX) models of HER2-amplified colorectal, esophageal and gastric cancers**

S. Peeren2, P. de Vries1, J. Piascik1, R. Rosler1

1Research and Development, Cascadian Therapeutics, Seattle, WA, USA

**Background**

Tucatinib, an orally bioavailable and HER2 selective small molecule tyrosine kinase inhibitor, is currently being developed for HER2 metastatic breast cancer in combination with capecitabine + trastuzumab (HER2CLIMB study). In addition to breast cancer, HER2 is amplified in subsets of patients with other malignancies, including gastrointestinal cancers (colorectal, esophageal and gastric cancers). To test whether tucatinib might have utility in treating HER2-amplified cancers originating from the gastrointestinal tract, tucatinib was tested alone, and in combination with trastuzumab, in cell line derived and PDX models of colorectal, esophageal and gastric cancer.

**Methods**

In vivo assays were performed to evaluate the combination of tucatinib and trastuzumab in HER2-amplified cell lines by measuring changes in signal transduction (pHER2, pHER3, pAKT) and cell survival. The in vivo activity of tucatinib (30 mg/kg BID) and trastuzumab (20 mg/kg QND) was evaluated alone, or in combination, in established HER2-amplified tumor models, including PDX models of colorectal, esophageal and gastric cancers.

**Results**

As a single agent, or in combination with trastuzumab, tucatinib demonstrated significant anti-tumor activity, including tumor regressions, in the N87 gastric cancer cell line xenograft model and in PDX models of HER2 amplified colorectal, esophageal and gastric cancers. The combination of tucatinib and trastuzumab was consistently more active than either single agent alone, and resulted in tumor growth inhibition from 85-139%, including complete tumor regressions in HER2+ gastric PDX models.

**Conclusions**

The activity of tucatinib in HER2-amplified colorectal, esophageal and gastric tumor xenograft models supports the exploration of using tucatinib to treat HER2+ gastrointestinal cancers in the clinical setting. To this end, an open-label phase IIb clinical study comparing tucatinib with or without trastuzumab in HER2+/RAS wild type metastatic colorectal cancer (MOUNTAINEER) has recently been initiated.

**Legal entity responsible for the study:** Cascadian Therapeutics

**Funding:** Cascadian Therapeutics

**Disclosure:** S. Peterson: Employee and shareholder of Cascadian Therapeutics, corporate officer of Cascadian Therapeutics. P. de Vries, J. Piascik, R. Rosler: Employee and shareholder of Cascadian Therapeutics.
Background: We built a risk classification model for resected SqCLC (R-SqCLC) by combining clinicopathological predictors to discriminate patients’ (pts) prognosis. We built a risk classification model for resected SqCLC (R-SqCLC) by combining clinicopathological predictors to discriminate patients’ (pts) prognosis. We built a risk classification model for resected SqCLC (R-SqCLC) by combining clinicopathological predictors to discriminate patients’ (pts) prognosis. We built a risk classification model for resected SqCLC (R-SqCLC) by combining clinicopathological predictors to discriminate patients’ (pts) prognosis.

Results: Main results of overall 97 pts (Training/Validation: 60/37) are presented in the Table.

Table: 1640P

<table>
<thead>
<tr>
<th>Gene</th>
<th>Training Set [%]</th>
<th>Validation Set [%]</th>
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<tbody>
<tr>
<td>TP53</td>
<td>53 [88.3]</td>
<td>27 [72.9]</td>
</tr>
<tr>
<td>TERT</td>
<td>4 [6.7]</td>
<td>2 [5.4]</td>
</tr>
<tr>
<td>PTEN</td>
<td>6 [10]</td>
<td>4 [10.8]</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>3 [5]</td>
<td>3 [8.1]</td>
</tr>
<tr>
<td>RICTOR</td>
<td>13 [35.1]</td>
<td>14 [23.3]</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>17 [45.9]</td>
<td>26 [43.3]</td>
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<tr>
<td>FGFR1</td>
<td>14 [37.8]</td>
<td>18 [30]</td>
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<tr>
<td>PTEN</td>
<td>5 [13.5]</td>
<td>19 [31.7]</td>
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The in vitro results support a significant inhibition of H-1703 cells proliferation by Gemcitabine, Docetaxel, PF-502138, MK-2206 and AZD2014 with IC50 values of 0.4 nM, 0.45 nM, 10 nM, 66 nM, 110 nM, respectively.

Conclusions: Our multi-step genomic analysis performed in almost 100 R-SqCLC pts allowed us to identify altered pathways with a biological impact in SqCLC oncogenesis, as the PIK3/RICTOR-mTORC2 axis. Moreover, our in vitro results justify pursuing mTOR inhibition, focusing on mTORC2 complex, in RICTOR-aberrant tumors.

Legal entity responsible for the study: Emilio Bria

Funding: My First AIRC (Associazione Italiana per la Ricerca sul Cancro) Grant (MFAG) project no. 14282. Young Investigational Award of the International Association for the Study of Lung Cancer (IASLC) 2015

Disclosure: All authors have declared no conflicts of interest.

PI3K/RICTOR-mTORC2 axis as a driver of prognosis and potential druggable target in squamous cell lung carcinoma (SqCLC) 6

Table 1640P

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<tr>
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The in vitro results support a significant inhibition of H-1703 cells proliferation by Gemcitabine, Docetaxel, PF-502138, MK-2206 and AZD2014 with IC50 values of 0.4 nM, 0.45 nM, 10 nM, 66 nM, 110 nM, respectively.

Conclusions: Our multi-step genomic analysis performed in almost 100 R-SqCLC pts allowed us to identify altered pathways with a biological impact in SqCLC oncogenesis, as the PIK3/RICTOR-mTORC2 axis. Moreover, our in vitro results justify pursuing mTOR inhibition, focusing on mTORC2 complex, in RICTOR-aberrant tumors.

Legal entity responsible for the study: Emilio Bria

Funding: My First AIRC (Associazione Italiana per la Ricerca sul Cancro) Grant (MFAG) project no. 14282. Young Investigational Award of the International Association for the Study of Lung Cancer (IASLC) 2015

Disclosure: All authors have declared no conflicts of interest.
limed is associated with TME modulation with increased T-cell infiltration. These data clearly support the combination of lefitolimod with checkpoint inhibitors in clinical trials.

Legal entity responsible for the study: Molengen AG

Funding: Molengen AG

Disclosure: K. Kapp, B. Voit, D. Oswald, M. Schmidt: Employee of Molengen AG. B. Wittig: Consults Molengen AG and also receives funding from Molengen AG.

1643P Circulating immune-profile as predictor of outcome in advanced NSCLC patients treated with nivolumab

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1Medical Oncology Unit, University Hospital of Parma, Parma, Italy; 2Department of Medicine and Surgery, University Hospital of Parma, Parma, Italy; 3Medical Oncology Unit, University Hospital Sant’Orsola, Bologna, Italy; 4Malattie Infettive ed Epatologiche, University Hospital of Parma, Parma, Italy

Background: Detection of predictive markers of anti-PD-1/PD-L1 antibodies activity is of pivotal interest in non-small cell lung cancer (NSCLC). This study aimed to identify circulating immune-profile as predictor of outcome in NSCLC patients treated with nivolumab.

Methods: A peripheral blood immune-profile evaluation was performed at baseline (T0), after 2 (T1) and 4 cycles (T2) of bi-weekly nivolumab in advanced pre-treated NSCLC patients from two Italian Institutions. First tumor assessment was performed after 4 cycles and then every 2 months. FACs analysis of lymphocyte subpopulations (CD3, CD4, CD8, NK, CD56), Treg (FOXP3) and MDSC was performed. Absolute and % changes of lymphocyte subsets together with the functional and proliferative activity were assessed. Qualitative quantitative leucocyte composition at baseline and its variation during therapy were correlated with tumor response and survival.

Results: In the overall population of 54 treated patients, baseline Neutrophil-to-Lymphocyte ratio and NK count, lymphocytes and CD3 variations during therapy showed a statistically significant prognostic role (p < 0.001; p = 0.012 < p < 0.001; p = 0.010, respectively). Among 31 patients (squamous carcinoma, n = 17; adenocarcinoma, n = 14) in which all 3 time points samples were available, 19 were responders (response and stable disease) and 12 non-responders. In responders, absolute numbers of total NK and NKCD56dim subset were higher at baseline and their increase between T0 and T1 was statistically significant (p < 0.05). Responders also displayed increased cytotoxic capability as shown by a higher baseline expression of CD107, perforin and granulocyte in NKCD56dim subset. No significant variation was documented in absolute number and functional activity of CD4+ and CD8+ lymphocytes. A higher percentage of CD8+ PD-1+ cells at baseline was observed in responders, while non-responders showed a statistically significant increase in the absolute number of MDSC during therapy (p < 0.05).

Conclusions: The number and functional of NKs and the frequency of PD-1 expression in CD8+ cells could represent predictive peripheral immune-biomarkers for nivolumab treatment in advanced NSCLC.

Legal entity responsible for the study: University Hospital of Parma

Funding: AIRG

Disclosure: All authors have declared no conflicts of interest.

1644P Monitoring the effect of cytostatic treatment by immune activity

TF. Hansen1, L. Nederby1, T. Bechmann1, E. Jakobsen1, A. Zedan1, I. Møhlom1, T. Herresen1, K. Steffensen1, C. Thomsen1, L. Raumkilde1, L.H. Jensen1, A. Jakobsen1
1Oncology, Vejle Hospital, Vejle, Denmark; 2Immunology and Biochemistry, Vejle Hospital, Vejle, Denmark

Background: Early prediction of effect remains an unsolved problem in cytostatic treatment of malignant tumors. The aim of the present study was to analyze the potential relationship between immune activity as measured by the NK Vue® system and response in patients with different tumors and different cytostatic regimens.

Methods: The study included six different trials encompassing patients with breast, prostate, ovarian and colorectal cancer. All protocols are still recruiting and so far 108 patients have been included. The preliminary results are based on 54 patients with response data available from the first evaluation. Blood samples were collected at baseline and prior to each treatment cycle into NK Vue® Promocla tubes and placed in an incubator at 37°C within 15 minutes of sampling. Following 24 hours of stimulation the plasma in each tube was harvested and analyzed for the level of interferon-gamma, as a surrogate for immune activity, by enzyme-linked immunosorbent assay using the NK Vue® Gold Kit.

Results: Similar results were seen between immune response and tumor types receiving different treatments. Consequently, data were pooled for preliminary evaluation. The outcome suggested a classification into three groups. The interferon-gamma dropped to an abnormal level (< 200 pg/ml) in group 1 (27 patients) or remained at an abnormal level during treatment. In group 2 (12 patients) the level remained within a normal range (> 500 pg/ml), while in group 3 (15 patients) it was raised from an abnormal to a normal level. The response rates were 11%, 42%, and 80% in the three groups, respectively. The difference was highly significant (p < 0.001). Accordingly, the positive and negative predictive values of a raising level were 80% and 54%, respectively.

Conclusions: The results suggest a relationship between the ability to mount an immune response upon stimulation and treatment effect comparable among different tumor types and treatments. Increasing levels of interferon-gamma shortly after initiation of treatment seems to predict treatment effect. Updated results will be presented at the meeting.

Legal entity responsible for the study: Vejle Hospital, Department of Oncology

Funding: ATGen

Disclosure: All authors have declared no conflicts of interest.

1644P Analysis of programmed death-ligand 1 (PD-L1) expression, transforming growth factor (TGF-b) gene expression signatures (GES) and tumor-infiltrating immune cells (IC) in hepatocellular carcinoma (HCC): Rationale for targeting PD-L1 and TGF-b

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1RGO Global Early Development, EMD Serono Research & Development Institute, Billerica, MA, USA; 2Bioinformatics, EMD Serono Research & Development Institute, Billerica, MA, USA; 3M-O-E-DP#1, Merck KGaA, Darmstadt, Germany; 4Clinical Biomarkers and Companion Diagnostics, EMD Serono Research & Development Institute, Billerica, MA, USA; 5Pathology, Institute of Pathology, University Hospital Basel, Basel, Switzerland; 6CBD, Merck KGaA, Darmstadt, Germany

Background: HCC evades antitumor immune responses via multiple mechanisms, including the PD-L1 and TGF-b pathways. PD-L1 expression correlates with tumor aggressiveness and recurrence. Increased TGF-b activity corresponds with poor clinical outcomes. Using immunohistochemistry (IHC), we previously showed that PD-L1 expression in HCC stems primarily from IC. To further assess the HCC immune milieu, we measured IC, TGF-b-associated GES, and PD-L1 expression using IHC/RNAseq.

Methods: We assessed protein expression in 50 selected HCC specimens by quantitative (Q) IHC (primary antibodies: PD-L1, CD8, CD68) using standard techniques and automated software. For RNAseq, we prepared strand-specific libraries from extracted RNA, which were sequenced and compared to GES from published papers, CIBERSORT and Ingenuity Pathway Analysis.

Results: All cases had typical morphology (i.e., high-grade trabecular, pseudoglandular, or solid with common cytoplasmic features). Q CD8 IHC significantly correlated with CD8 mRNA expression and CD8+ T cell GES, supporting the utility of RNAseq to evaluate the role of CD8+ T cells in HCC. RNAseq identified TGF-b1 as the main TGF-b isoform in HCC. Predefined TGF-b GES correlated strongly with EMT GES. There was a trend toward increased TGF-b1 activity and EMT marker expression in the SI molecular subtype, which has previously been associated with TGF-b-driven aberrant Wnt signaling. Q CD8+ HCC correlated with PD-L1 mRNA and protein levels in IC. In samples with high CD8+, there was a trend of increased tumor-associated macrophages (TAMs); the presence of TAMs strongly correlated with TGF-b GES. Interestingly, few tumor cells displayed membranous PD-L1 staining as confirmed by PD-L1/pan-cytokeratin double labeling.

Conclusions: We used RNAseq and IHC to better understand the immunosuppressive environment in HCC driven by TGF-b and PD-L1, which may mediate different mechanisms to inhibit preexisting CD8+ T cells.

Clinical trial identification: N/A

Legal entity responsible for the study: Funding was provided by Merck KGaA, Darmstadt, Germany.

Funding: Funding was provided by Merck KGaA, Darmstadt, Germany. Disclosure: Y. Zhang, B.J. Naughton, P.A. Roffe, I. Dussault: Employee of EMD Serono Research & Development Institute, Billerica, MA, USA. E. Frick-Krieger: Employee of Merck KGaA, Darmstadt, Germany. L. Terracciano: Consulting/advisory role to Merck AG.

1646P Clinical factors associated with mutation burden in non-small cell lung cancer

1Thoracic Oncology, Shizuoka Cancer Center, Shizuoka, Japan; 2Research Institute, Shizuoka Cancer Center, Shizuoka, Japan; 3Clinical Research Promotion Unit, Shizuoka Cancer Center, Shizuoka, Japan; 4Thoracic Surgery, Shizuoka Cancer Center, Shizuoka, Japan; 5Diagnostic Pathology, Shizuoka Cancer Center, Shizuoka, Japan; 6Hospitalect and Research Institute, Shizuoka Cancer Center, Shizuoka, Japan

Background: Mutation burden (MB) analysis is scarce in routine clinical practice. We aimed to identify predictive factors for amount of MB in patients with resected non-small cell lung cancer (NSCLC).

range (>500 pg/ml), while in group 3 (15 patients) it was raised from an abnormal to a normal level. The response rates were 11%, 42%, and 80% in the three groups, respectively. The difference was highly significant (p < 0.001). Accordingly, the positive and negative predictive values of a raising level were 80% and 54%, respectively.

Conclusions: The results suggest a relationship between the ability to mount an immune response upon stimulation and treatment effect comparable among different tumor types and treatments. Increasing levels of interferon-gamma shortly after initiation of treatment seems to predict treatment effect. Updated results will be presented at the meeting.

Legal entity responsible for the study: Vejle Hospital, Department of Oncology

Funding: ATGen

Disclosure: All authors have declared no conflicts of interest.
Table: 1646P Genetic alterations according to histologic subtype (N = 150).

<table>
<thead>
<tr>
<th>ADC</th>
<th>n = 59 (100%)</th>
<th>MET amp</th>
<th>n = 62 (100%)</th>
<th>SaC</th>
<th>n = 19 (100%)</th>
</tr>
</thead>
<tbody>
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<td>KRAS</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>mut (exons 2-3)</td>
<td>14 (20%)</td>
<td>GA 3 (5%)</td>
<td>Mu 1 (5%)</td>
<td>wt 16 (94%)</td>
<td></td>
</tr>
<tr>
<td>wt</td>
<td>45 (80%)</td>
<td>NC 53 (85%)</td>
<td>wt 12 (63%)</td>
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</tr>
<tr>
<td>EGFR</td>
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<tr>
<td>mut (exons 18-21)</td>
<td>6 (10%)</td>
<td>Mut 0 wt 12 (63%)</td>
<td>wt 15 (79%)</td>
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<tr>
<td>wt</td>
<td>49 (83%)</td>
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<tr>
<td>Unknown</td>
<td>4 (7)</td>
<td>Unknown 4 (6) wt 15 (79%)</td>
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<tr>
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<tr>
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<td>7 (12)</td>
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<tr>
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<td>4 (7)</td>
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<tr>
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<td>4 (7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>wt</td>
<td>55 (93)</td>
<td></td>
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<tr>
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<td>4 (7)</td>
<td></td>
<td></td>
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<td>1 (2)</td>
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</table>

Methods: We assessed somatic MB in surgical tumor specimens with whole exome sequencing (WES) using an ion torrent proton platform (Thermo Fisher Scientific). Two hundred forty-six NSCLC patients were randomly divided into training (n = 123) and validation (n = 123) cohorts. We defined patients with a greater than median number of non-synonymous (n-syn) mutations as the higher MB group. To detect higher n-syn MB in the training cohort, digital data was assessed using a stepwise regression model. The validation cohort was subsequently analyzed. Also, the detected factors were validated via 100 repetitions of this procedure with different randomly divided cohorts using bootstrapping method.

Results: Out of 250 NSCLC patients with tumors surgically resected between September 2014 and September 2015, we analyzed tumors from 246 patients. Patient background: median age (range) 78 (59-87), male 63%, smoker 71%, pathological stage (p-stage) (I/II/III) 67/21/12% respectively, histological type (Ad/Sq) 78/22%, EGFR mutation (positive/wild type) 31/69%, median serum CEA level (range) 3.3 ng/ml (0.5-491.8), median serum CYFRA 21-1 level (range) 1.22ng/ml (1-38), median exonic MB (range) 82.5 (4-2144) [1.79 mt/Mb (0.1-61.4)], and median n-syn MB (range) 41 (1-1510) [1.17 mt/Mb (0.02-43.2)]. Stepwise regression analysis identified four factors (histological type: squamous, smoking status: smoker, age: greater than or equal to 70, and elevated serum CEA level) associated with high n-syn MB. The area under the curve for the four variables in the training and validation cohorts was 0.82 and 0.84, respectively. Squamous histology, smoker, and elevated CEA level showed highly reproducible in repeated random simulations (p = 0.093, 1.8, and 0.72). The receiver operating characteristic curves predicting high MB, the area under the curve for the four variables in the training and validation cohorts was 0.82 and 0.84, respectively. Squamous histology, smoker, and elevated CEA level showed highly reproducible in repeated random simulations (p = 0.093, 1.8, and 0.72).

Conclusions: Along with squamous histology and smoking, elevated CEA level may be an independent predictive factor for higher MB in NSCLC.

Legal entity responsible for the study: Shizuoka Cancer Center

Funding: None

Disclosure: All authors have declared no conflicts of interest.
KRAS mutant tumors according to additional co-mutations: 25% of KRAS+STK11 were PD-L1+ whereas 75% of KRAS+TP53 were PD-L1+, despite no statistically significance.

Conclusions: MET and STK11 alterations were correlated with differential expression of tumor PD-L1. STK11 mutant tumors were more likely to have an immunosuppressive phenotype. Tumors harbouring specific genomic alterations might be enriched for distinct immunophenotypes which might contribute to rational use of immunotherapeutics.

Legal entity responsible for the study: IDIBELL- Institut Català d’Oncologia

Funding: None

Disclosure: All authors have declared no conflicts of interest.

B7-H3 (CD276) on circulating epithelial tumor cells (CETCs) correlates with proliferation marker Ki-67 and may be associated with aggressiveness of tumor in breast cancer patients

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Tobias Beyer, Bayreuth, Germany

Background: CETCs in the peripheral blood are a prerequisite for the development of metastases. B7-H3 is an important immune checkpoint member of the B7 family and inhibits T-cell mediated anti-tumor immunity. It is highly overexpressed on a wide range of solid cancers and often correlates with both negative prognosis and poor clinical outcome in patients. Based on the clinical success of the novel immune checkpoint blockade, mAbs against B7-H3 appear to be promising therapeutic strategy. In order to better understand the role of B7-H3 in cancer development we used a non-invasive, real-time biopsy for determining B7-H3 on CETCs in breast cancer patients.

Methods: Blood from 50 patients suffering from breast cancer were analyzed for CETCs. The number of vital CETCs and the expression of B7-H3 and Ki-67 were evaluated using the maintrac® method.

Results: CETCs were detected in all examined patients (ranged from 2-676 CETCs in 100 μl of blood). B7-H3 expression on the surface of CETCs was found in 82% of patients. Triple negative breast cancer patients had statistically significantly more B7-H3 positive CETCs than patients with hormone receptor positive tumor tissue (median 50 vs. 26.3, p < 0.05). The frequency of B7-H3 positive CETCs was significantly higher in patients who received radiation therapy compared to patients without irradiation (mean 42 vs. 29, p < 0.05). B7-H3 positive CETCs seem to be more aggressive because the percentage of B7-H3 positive CETCs correlated with the percentage of proliferation marker Ki-67 positive CETCs (r = 0.689 and p < 0.001). Interestingly, a significant relationship between Ki-67 expression level on the CETCs and nodal status was found.

Conclusions: Breast cancer patients that detectable CETCs with high frequency of B7-H3 expression regardless of stage of disease. B7-H3 seems to be an important factor in immune evasion and may be a promising target of anticancer therapies. Furthermore, radiation leads to up-regulation of B7-H3 expression on CETCs, which could be a possible mechanism of acquired radio-resistance.

Legal entity responsible for the study: N/A

Funding: None

Disclosure: U. Pachmann, K. Pachmann: Holder of patent. All other authors have declared no conflicts of interest.

Survival of non-small cell lung cancer patients predicted from expression of PD-L1, HLA class I and MICA/B on tumor cells


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Background: Several groups have reported that programmed death-1 (PD-1) ligand 1 (PD-L1) overexpression on tumor cells predicts a poor prognosis in patients with non-small cell lung cancer (NSCLC). Although recent studies have shown that PD-L1 overexpression on tumor cells predicts for improved clinical outcome in NSCLC patients treated with anti-PD-1/PD-L1 immunotherapy, PD-L1 low/negative tumors also benefit from anti-PD-1/PD-L1 immunotherapy. These findings suggest that study on multi-immune parameters should be considered. We recently reported that the overexpression of PD-L1 in tumor predicted a poor prognosis while overexpression of CD14+ monocytes by 1.9 fold (p < 0.01) after 1 h, and 4.9 fold (p < 0.01) after 3 h that was comparable with the effect of MCP-1. In vitro tube formation assays using HUVEC cells demonstrated that YKL-39 has a strong pro-angiogenic effect. In human samples of breast cancer YKL-39 was found to be expressed in CMECs but not in cancer cells or other stromal cell types. In breast cancer biopsy specimens it was found that high YKL-39 gene expression correlated with the significantly reduced frequency of lymphatic and hematogenous metastasis. Furthermore, high level of YKL-39 expression associated with 100% metastatic-free survival rate (p < 0.015). However, its biological activity and association with tumor progression remains unknown.

Results: Human monocytes-derived macrophages differentiated in the presence of IL4 and TGFbeta3, but not IL4 alone, were found to express high levels of YKL-39 mRNA and protein. Purified YKL-39 significantly enhanced the migration of human CD14+ monocytes by 1.9 fold (p < 0.01) after 1 h, and 4.9 fold (p < 0.01) after 3 h that was comparable with the effect of MCP-1. In vitro tube formation assays using HUVEC cells demonstrated that YKL-39 has a strong pro-angiogenic effect. In human samples of breast cancer YKL-39 was found to be expressed in CMECs but not in cancer cells or other stromal cell types. In breast cancer biopsy specimens it was found that high YKL-39 gene expression correlated with the significantly reduced frequency of lymphatic and hematogenous metastasis. Furthermore, high level of YKL-39 expression associated with 100% metastatic-free survival rate (p < 0.015). However, its biological activity and association with tumor progression remains unknown.

Conclusions: TGFbeta is a key cytokine inducing production of YKL-39 in macrophages. YKL-39 stimulates critical for tumor progression processes: chemotaxis of monocytes and angiogenesis. However high levels of YKL-39 expression in tumor samples are predictive for metastatic-free survival in patients with breast cancer, suggesting that YKL-39 can program monocytes and newly growing vessels to inhibit metastatic spread. This study was supported by grant RFN N14-15-00350.

Legal entity responsible for the study: Tomsk State University, Tomsk, Russian Federation

Funding: Tomsk State University, Tomsk, Russian Federation

Disclosure: All authors have declared no conflicts of interest.

Pre-treatment neutrophil lymphocyte ratio/platelet lymphocyte ratio as surrogate markers of survival in non-metastatic head and neck cancer patients: An observational study

V. Aragwal1, R. Rao2, H. Abin3, V. Rao4, R.C. Nayar4, V. Mani2, A. Ram2, B.S. Ajaykumar1

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Background: Neutrophil lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are known to be surrogate markers of inflammation and have been shown to predict mortality in patients with heart disease and cancer. In this study, we evaluate the
influence of pre-treatment NLR and PLR on overall survival in head and neck cancer patients.

Methods: In this observational correlational study, subjects with a diagnosis of non-metastatic head and neck cancer were included. The mean age of the study sample was 64.8 years. Forty-two percent of study participants underwent surgery, while 34% underwent concurrent chemoradiation. Neoadjuvant chemotherapy was given to 24.4% of patients.

Results: In the study population, neutrophil-lymphocyte ratio and platelet-lymphocyte ratio had a statistically significant positive correlation with the risk of postoperative recurrence.

Conclusions: These findings suggest that NLR and PLR may be useful markers for predicting postoperative recurrence in patients with non-metastatic head and neck cancer.
lymphatic metastasis. Our aim was to analyse the effect of NAC on correlation of TAM in intrauterine compartments with angiogenesis and lymphangiogenesis.

Methods: 115 female patients with breast cancer T1-4N0-M0 were included in the study. 36 patients did not receive NAC, 79 received NAC. Expression levels of CD68 (general macrophage marker), stabilin-1 (marker of M2 macrophages), CD31 (marker of blood vessels) and LYVE1 (marker of lymphatic vessels) were identified by immunohistochemistry in 5 distinct areas of tumors: 1) soft fibrous stroma; 2) coarse fibrous stroma; 3) areas of maximum stromal-and-parenchyma relationship; 4) parenchymal elements; 5) gaps of ductal tumor structures.

Results: In breast cancer samples of patient who did not receive NAC direct correlation of CD68 expression in soft fibrous stroma and CD31 expression in coarse fibrous stroma (r = 0.8, p = 0.01) was identified. However, reverse correlation was found between CD68 expression in gaps of ductal tumor structures and LYVE1 expression in soft fibrous stroma (r = -0.89, p = 0.04). In contrast, in patients after NAC we identified a direct correlation between expression of CD68 and LYVE1 expression in the gaps of ductal tumor structures (r = 0.80, p = 0.02). Expression of stabilin-1 in coarse fibrous stroma directly correlated with amount of LYVE1 + cells in areas with maximum stromal-and-parenchymal relationship (r = 0.76, p = 0.04), but reversely correlated with the amount of CD31 + vessels in soft fibrous stroma (r = -0.52, p = 0.001).

Conclusions: Our data suggest that TAM before treatment support tumor angiogenesis however protect against lymphangiogenesis. After NAC TAM can switch their functional phenotype, do not support angiogenesis anymore but support lymphangiogenesis. The mechanism of chemotherapeutic programming of TAM remains to be identified. This study was supported by grant RNF N14-15-00350.

Legal entity responsible for the study: Tomsk State University, Tomsk, Russian Federation.

Funding: Tomsk State University, Tomsk, Russian Federation. This study was supported by grant RNF N14-15-00350.

All authors have declared no conflicts of interest.
Conclusions: Isolated BRCA1 proficient cells are still present in cheemo-naive carcinoma with BRCA1 LOH, indicating that the somatic loss of the wild-type BRCA1 is not necessarily the first event in the pathogenesis of hereditary OC. These clones rapidly expand during even the early stage of systemic therapy. BRCA1-deficient cells have selective advantage in the absence of drug exposure and repopulate the tumor mass during platinum-free intervals. These fluctuations of BRCA1 LOH status explain why conventional platinum-based therapy, being capable to produce excellent tumor responses in BRCA1 germline mutation carriers, is not curative when considering long-term outcomes.

Legal entity responsible for the study: Laboratory of Molecular Oncology, N.N. Petrov Institute of Oncology, St.-Petersburg

Funding: Russian Scientific Fund (grant 14-25-01111)

Disclosure: All authors have declared no conflicts of interest.

Methods: To study the cooperation of Atm in prostate cancer progression in vivo, we crossed the transgenic mouse model TRAMP with Atm null mice in C57BL/6 background. This model allo ws us to elucidate the presence of tumors in wild-type (+/−), heterozygous (+/−), and homozygous (−/−) Atm loss in mice. PIN, invasive and metastatic prostate cancer as well as survival curves were compared for the three arms. In addition, in a large cohort of mCRPC (n = 419) from the prospective PROPEPAIR-B study (NCT03075355), in which a large panel of germline DNA repair genes were studied, we compared the clinico-pathological characteristics at baseline and mCRPC diagnosis between germline ATM mutation carriers and non-ATM carriers. Chi-Square and Exact Fisher test, the Kaplan-Meier method and Long-rank test were used for statistical analyses.

Results: Twenty eight TRAMP+/−; Atm+/−/+; and 45 TRAMP+/−; Atm−/−/+ mice were follow-up until sacrifice-endpoint. Heterozygous Atm loss mice presented higher frequency of metastasis in the necropsy compared to Atm wild-type (44% vs. 21%, p = 0.045) and shorter median survival (26 vs. 32 weeks, p = 0.008). There were not significant different observed in PIN or invasive tumour prevalence. TRAMP−/−; Atm−/−/+ mice were excluded from analyses due to the early development of lethal thymus requiring sacrifice before week 16. On the other hand, 8 patients out of 419 were found to harbour germline pathogenic ATM mutations (1.9%), and compared with non-ATM carriers presented higher frequency stage IV at diagnosis (63% vs. 34%, p = 0.2), bone metastasis (100% vs. 82%, p = 0.4) without other relevant differences found in these preliminary analyses.

Conclusions: Aberration in the ATM gene may favour metastatic progression in PrCa in prostate cancer preclinical models, although its clinical implication will require further clarification in the future.

Clinical trial identification: Part of the results came from the prospective PROPEPAIR-B study (NCT03075355)

Legal entity responsible for the study: Spanish National Cancer Research Centre

Funding: Prostate Cancer Unit-Spanish National Cancer Research Centre

Disclosure: All authors have declared no conflicts of interest.

Methods: Using in vitro studies we demonstrated that depletion of CEP55 sensitizes TRAMP cells to anti-mitotic drugs like PLK1 inhibitor to induce Cdk1-Caspase 3-dependent mitotic catastrophe due to unscheduled Cdk1/Cyclin B activation. Also we showed ERK1/2 transcriptionally controls CEP55 hence inhibition of MEK1/2 using the small molecule inhibitor Selumetinib can mimic depletion of CEP55 in vivo.

Results: We rationalised the usage of a MEK1/2 inhibitor in combination with a PLK1 inhibitor across a series of BC cell lines. We observed synthetic lethality among the aggressive hormone receptor negative lines with higher CEP55 expression compared to normal like and receptor positive lines with lower CEP55 level. The combination synergistically amplified apoptosis of aneuploid population via premature entry of these cells into mitosis in the presence of antimitotic drugs due to exhaustion of CEP55. We have also validated this synergistic effect of MEK1/2 and PLK1 inhibition using xenograft models, results of which imitated the in vitro findings.

Conclusions: We propose a novel treatment tactic of MEK1/2-PLK1 dual combination for selectively targeting CEP55 over-expressing BC in the clinic.

Legal entity responsible for the study: QIMR Berghofer Medical Research Institute

Funding: Cancer Council Queensland (CCQ) and National Health & Medical Research Council

Disclosure: All authors have declared no conflicts of interest.

Methods: Synergistic inhibition of CEP55 induces mitotic catastrophe and specifically targets aggressive breast cancer

1661P

Synergistic inhibition of CEP55 induces mitotic catastrophe and specifically targets aggressive breast cancer

D. Suria, M. Kalmutho, A.J. Lopez, K.K. Khanna

Cell and Molecular Biology, QIMR Berghofer Medical Research Institute, Brisbane, Australia

Background: Triple negative breast cancers (TNBCs) are the most aggressive and poorly heterogenous form of breast cancer (BC), treatment of which is a prevalent challenge faced in clinics. CEP55, discovered first by our laboratory, is a key regulator of cytokinesis, error in which roots to multi-nucleation. Function of CEP55 is critically delimited by ERK2/PLK1 dependent phosphorylation, for accurate cytokinesis. Research has demonstrated connotation of CEP55 with numerous cancers including BC as higher CEP55 mRNA expression is allied to worse prognosis and poor survival.

We hypothesised that, CEP55 controls fate of aneuploid cell population among agressive BC that are heavily reliant on mitotic genes for tumour progression, thus can be targeted for therapy development.

Methods: Using in vitro studies we demonstrated that depletion of CEP55 sensitizes TRAMP cells to anti-mitotic drugs like PLK1 inhibitor to induce Cdk1-Caspase 3-dependent mitotic catastrophe due to unscheduled Cdk1/Cyclin B activation. Also we showed ERK1/2 transcriptionally controls CEP55 hence inhibition of MEK1/2 using the small molecule inhibitor Selumetinib can mimic depletion of CEP55 in vivo.

Results: We rationalised the usage of a MEK1/2 inhibitor in combination with a PLK1 inhibitor across a series of BC cell lines. We observed synthetic lethality among the aggressive hormone receptor negative lines with higher CEP55 expression compared to normal like and receptor positive lines with lower CEP55 level. The combination synergistically amplified apoptosis of aneuploid population via premature entry of these cells into mitosis in the presence of antimitotic drugs due to exhaustion of CEP55. We have also validated this synergistic effect of MEK1/2 and PLK1 inhibition using xenograft models, results of which imitated the in vitro findings.

Conclusions: We propose a novel treatment tactic of MEK1/2-PLK1 dual combination for selectively targeting CEP55 over-expressing BC in the clinic.

Legal entity responsible for the study: QIMR Berghofer Medical Research Institute

Funding: Cancer Council Queensland (CCQ) and National Health & Medical Research Council

Disclosure: All authors have declared no conflicts of interest.

Methods: Synergistic inhibition of CEP55 induces mitotic catastrophe and specifically targets aggressive breast cancer

1660P

ATM role in prostate cancer (PrCa) progression and survival

V. Cerezo Fernández1, P. Nombela Blanco2, A. Medina1, N. Romero Lauwen1, J. Puente2, P.P. López Cano3, A. Gutiérrez Pecharromán1, R. Sanchez-Escudero3, L. Magraner3, E. Gallardo Díaz1, N. Lainez1, P. Jiménez Gallego4, R. Lozano Mejórraga1, E. Almagro Casado1, R. Luque Caro1, M. Domenech1, A.J. Lopez5, A. Hernández Jorge5, E. Castro Marcos1, M.D.P. González6, R. Sanchez-Escribano7, L. Magraner3

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Background: Germline and/or somatic aberrations in ATM gene have been recently identified in up to 5% of PrCa cases. It has been also described that mutations in DNA repair genes predispose individuals to more aggressive and lethal phenotypes. For these reasons, our goal is to investigate the role of ATM in PrCa progression.

Results: In the present study, ATM expression and gene copy number were evaluated in 487 PrCa patients from the Spanish National Cancer Research Centre-TRAMP (NCT03075355) cohort and in 134 untreated CaP patients from the PrCa datasets. ATM expression was lower in patients with higher clinical stage and in cases with bone metastasis. The ATM expression was also lower in cases presenting more aggressive histological features. ATM gene copy number was undetermined in 25 out of 487 patients, 100 (20.6%) PrCa patients presented a gene copy number of two, 187 (38.4%) showed copy number of three, 124 (25.5%) two copies, and 66 (13.5%) one copy. The ATM gene copy number was lower in cases with bone metastasis and higher expression of EGFR, and lower expression of Androgen Receptor. ATM gene copy number was also lower in cases with higher clinical stage.

Conclusions: In PrCa patients, ATM expression was associated with clinical stage, bone metastasis, and histological features. ATM gene copy number was associated with clinical stage and with bone metastasis. This study supports the role of ATM in the progression of CaP.
metastasis. OT-101 (Trabedersen) is a phosphorothioate ASO designed to specifically target human TGF-β2 mRNA. Herein, we report the synergizing effect of OT-101 in chemotherapy in mouse pancreatic tumor xenograft models for further exploration of clinical combination strategies.

Methods: OT-101 was administered as single agent (1-64 mg/kg, qd3xwk or qdx21) and in combination with Gemcitabine (GEM, 15 mg/kg, qdx2wk), Dacarbazine (DTIC, 1-10 mg/kg, qdx4wk) or Paclitaxel (PTX, 10 mg/kg, qdx5) to nude mice (10/ subgroup). We analyzed either (i) orthotopic human L3.6pl pancreatic cancer (PAC), (ii) human metastatic B161 melanoma, (iii) SC glioblastoma (U87) or (iv) SC ovarian (SKOV-3) tumors. Mice were monitored for adverse effects, body weight loss, tumor size and survival outcome. LYMPH node and liver surface and micro-metastases as well as size and weight of the pancreatic tumors were determined. Tumor sections were stained with anti-BrdUrd and CD31 antibodies to determine tumor cell proliferation and vascularization, respectively.

Results: OT-101 significantly reduced tumor growth (p = 0.0084), lymph node metastasis (p = 0.023), and tumor angiogenesis (p<0.0001) versus untreated control in the PAC model. OT-101 demonstrated synergy in tumor growth inhibition and increased survival in human malignant melanoma (B16F10, p = 0.038, vs. DTIC alone), glioblastoma (U87, p = 0.001 vs. PTX) and ovarian SKOV-3, p < 0.05 vs. PTX) cancer models when combined with either DTIC (B16F10) or PTX (U87 and SKOV-3). No synergy was observed with GEM (PAC). The combination regimen tested was effective and tolerable. Significant antitumor activity was achieved at aED of 80 mg/m²/day which is well below the optimized clinical dose used for IV infusion of patients at 140 mg/m²/day.

Conclusions: The preclinical data laid the groundwork for establishing combination therapies in the clinic. Of interest is the preferential synergy between OT-101 and PTX or PTX or DTIC, but not with GEM.

Legal entity responsible for the study: Autolec Inc

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1663P Targeting thioredoxin reductase 1 in novel combination therapies in p53 mutant triple negative breast cancer

P. Banerjee 1, M. Kalmuthu 1, D. Sinha 1, A. Bain 1, K. Tonissen 2, K.K. Khanna 1

1Cell and Molecular Biology, QIMR Berghofer Medical Research Institute, Brisbane, Australia, 2School of Natural Sciences, Griffith University, Brisbane, Australia

Background: The TP53 gene is frequently mutated in human cancers including triple negative breast cancers (TNBCs) (~84% patients). Although TP53 mutation is the only oncogenic driver in TNBC, no targeted therapies for mutant p53 (p53(TMB)) TNBCs are available. We aim to identify novel therapeutic targets and combination therapies for p53(TMB) TNBCs.

Methods: A large-scale genomic analysis was performed using the TCGA database to analyse the expression of various antioxidant genes in M1 and wild-type (wt) p53 BC cells. Thioredoxin reductase 1 (TrxR1) protein levels and redox activity were measured by western blot and DTNB reduction assay, respectively. M1 and wt p53 cells were treated with gold-based TrxR1 inhibitor and APR-246 and subsequently analysed for cell proliferation, apoptosis, and cell cycle progression. Phospho-histone H3 (pH3) Ser10 expression was analysed by FACS.

Results: We observed significant upregulation of TrxR1, a redox gene, in p53(TMB) BC patients compared to wt patients. TrxR1 protein levels and redox activity were higher in p53(TMB) cells compared to wt cells. Notably, TrxR1 inhibition selectively induced apoptosis in p53(TMB) BC cells, but not in wt cells. Upon treatment with TrxR1 inhibitor, a significant proportion of p53(TMB) cells arrested in the G2/M phase with a concomitant increase in pH3H3 Ser10, a marker of mitotic chromatin condensation. Thus, TrxR1 inhibition may lead to significant increase of BC cell death by causing mitotic catastrophe. APR-246, known to restore redox activity of p53(TMB) in many cancers, alone failed to induce apoptosis in p53(TMB) BC cells. However, co-treatment of APR-246 with a sub-lethal concentration of TrxR1 inhibitor resulted in a synergistic effect in p53(TMB) cells.

Conclusions: Inhibiting TrxR1 may represent an effective therapeutic strategy for p53(TMB) TNBCs. These results warrant a clinical evaluation of a novel combination therapy using APR-246 and TrxR1 inhibitors for p53(TMB) TNBC patients.

Legal entity responsible for the study: QIMR Berghofer Medical Research Institute

Funding: National Health and Medical Research Council, Australia

Disclosure: All authors have declared no conflicts of interest.

1664P Liprin-α4 could be a potential therapeutic target for pancreatic cancer

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Background: In pancreatic cancer whose microenvironment is extremely hypoxic condition, the analysis of signal transduction under hypoxia is thought to be significantly important. By investigating microarray analysis of pancreatic cancer cultured between under normoxia and hypoxia, we found that the expression of leukocyte common antigen related (LAR)- interacting protein (liprin-α4) was extremely increased under hypoxia compared to under normoxia. In the present study, the biological significance of liprin-α4 in pancreatic cancer was investigated and whether liprin-α4 could be a therapeutic target for this refractory cancer was estimated.

Methods: Three pancreatic ductal adenocarcinoma cell (PDAC) lines (ASPC-1, SUIT-2, and PANc-1) were cultured under normoxia (20%O2) and under hypoxia (1%O2), and were used as target cells. Inhibition of liprin-α4 was performed using liprin-α4 siRNA. Expression of liprin-α4 was analyzed by real time RT-PCR, western blot and immunofluorescent staining. Proliferation was estimated by cell count and MTT assay. Invasion was estimated by matrigel invasion assay. Mice xenograft experiments were performed using BALB/c nude female mice. Surgically resected human pancreatic cancer specimens were used for immunostaining.

Results: 1) Expression of liprin-α4 was increased in PDAC under hypoxia compared to normoxia. Hypoxia suppression decreased invasion through inhibition of endothelial mesenchymal transition in PDAC under hypoxia. 2) Liprin-α4 inhibition decreased proliferation of PDAC under hypoxia In vitro. 4) Tumor volume in mice injected with liprin-α4-inhibited PDAC was significantly lower than that in control mice. 5) Signaling from liprin-α4 was through PI3K and MAPK signaling pathways. 6) Relation between hypoxia inducible factor-1α (HIF-1α) expression and liprin-α4 expression was observed by immunofluorescent staining using surgically resected pancreatic cancer specimens.

Conclusions: These results suggest that liprin-α4 which is more expressed under hypoxia, plays pivotal role for inducing malignant phenotype such as proliferation and invasion in pancreatic cancer, and that liprin-α4 could be an effective therapeutic target for pancreatic cancer.

Legal entity responsible for the study: Cancer Therapy and Research, Kyushu University Hospital

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1665P Dual targeting of cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE) by miR-4317 displays a synergistic efficacy in repressing breast cancer progression

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Background: Recently, hydrogen sulphide (H2S) and its synthesizing enzymes, CBS and CSE, have been casted as pleiotropic regulators in the malignant transformation process. H2S paradoxically acts as oncogenic mediator in ovarian and liver cancers, and as tumor suppressor in prostate and gastric carcinomas. However, the link between H2S and Breast cancer (BC) remains unclear. Thus we aimed at unraveling the association between H2S and its synthesizing enzymes in BC progression. Furthermore, it was essential to evaluate their possible adoption as therapeutic targets in BC through their dual targeting by short non-coding RNAs.

Methods: Breast tissues were collected from 30 BC patients. K067 levels were quantified using immunohistochemistry. MDA-M2-231 and MCF7 cells were cultured and transfected with different oligonucleotides and/or treated with NaHS, an exogenous source of H2S. Total RNA was extracted and quantified by qRT-PCR. Cellular viability, proliferation, and migration were measured using MTT, BrDU and scratch assays respectively. Bioinformatic analysis was performed to predict novel miRNAs that could target both CBS and CSE.

Results: CBS and CSE were significantly upregulated in BC tissues. Patients with high K067 scores showed the highest expression levels of CBS and CSE. Knocking down of CBS and CSE using siRNAs resulted in a significant attenuation of different hallmarks of BC. On the other hand, NaHS resulted in an increase in BC progression. miR-4317 was found to putatively target both CBS and CSE oncogenes with high binding scores. Ectopic expression of miR-4317 in BC cell lines resulted in a simultaneous reduction of CBS and CSE transcripts which was associated with a concomitant reduction in cellular viability, proliferation and migration. Finally, co-treatment of miR-4317 and NaHS resulted in abrogation of miR-4317 tumor suppressor activity.

Conclusions: This study showed a marked upregulation of CBS and CSE in BC tissues and characterized them as aggressive oncogenic drivers in BC. Moreover, miR-4317, a novel tumor suppressor in BC, displayed a synergistic effect in halting BC progression via twin-targeting CBS and CSE and diminishing H2S levels in BC cell lines.

Legal entity responsible for the study: German University in Cairo

Funding: None

Disclosure: All authors have declared no conflicts of interest.
**Annals of Oncology**

**1668P Met/Axl system as a dual target in the mesothelioma pathway and invasiveness**

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**Background:** Malignant pleural mesothelioma is an aggressive and highly lethal disease. Conventional chemotherapies and radiation therapy have limited efficacy. Many evidences suggest the roles of receptors tyrosine kinase (RTKs) in mesothelioma pathogenesis, in particular epidermal growth factor (EGFR), Met and Axl. Axl activation is involved in proliferation and inhibition of apoptosis, and its over-expression represents a key molecular determinant underlying the development of acquired resistance to targeted anticancer agents.

**Methods:** Different histological types, epithelioid, sarcomatoid and mixed, of human mesothelioma cell lines were used. Protein levels of Met, Axl and its ligand, growth arrest-specific 6 (Gas6) were evaluated by Western blot analysis. We conducted in vitro treatments with different doses of Foretinib, dual inhibitor of Met and Axl, in order to demonstrate the variation of cell proliferation and migration through MTI and Colony Forming Assay at the range dose 0.1-1 μM of Foretinib. Lastly, the rate of cell apoptosis was quantified by flow cytometry.

**Results:** The presence of Met, Axl and Gas6 proteins were found in all cell lines analyzed with different expression pattern. The dose escalation of Foretinib from 0.01 μM to 2 μM strongly inhibited cell proliferation and migration of mesothelioma cell lines. Treatment with Foretinib (at the dose 0.5 μM and 1 μM), determining a significantly increase of apoptosis rate (up to 50%) in specific histological type suggesting a different cell senibility.

**Conclusions:** The co-activation of MET and AXL in mesothelioma cell lines suggests that these kinases could serve as novel therapeutic targets. MET and AXL inhibitors could be used as novel anticancer therapies influence clinically meaningful endpoints including metastatic recurrence and survival in the majority of tumour types.

**Legal entity responsible for the study:** University of Campania “Luigi Vanvitelli”

**Funding:** Associazione Italiana per la Ricerca sul Cancro (AIRC)

**Disclosure:** All authors have declared no conflicts of interest.

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**1667P Targeting CXCR4 and FAK in non-small cell lung carcinomas with co-inactivated p53 and PTEN tumor suppressors**


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**Background:** In this study we evaluated potential of targeting CXCR4 and focal adhesion kinase (FAK) in suppressing metastatic spread of p53/PTEN deficient non-small cell lung carcinomas (NSCLCs).

**Methods:** We first examined the invasive characteristics of NSCLC cells with suppressed p53 and PTEN activity using wound healing, gelatin degradation and invasion assays. Namely, NCI-H460 cells with applied pharmacological inhibition of wild type p53 and PTEN activity (NCI-H460-mt/mt) were analyzed along with COR-L23 cells that have intrinsically inactive both tumor suppressors. Further, changes in the expression of CXCR4 and FAK were evaluated by RT-qPCR and Western Blot analysis. Finally, we tested the ability of CXCR4 and FAK inhibitors (WZ811 and PF-573228, respectively) to suppress the migratory and invasive potential of p53/PTEN deficient NSCLC cells, in vitro and in vivo using orthotopic metastatic lung carcinoma mouse model.

**Results:** Our results showed that cells with mutually inactive p53 and PTEN have significantly increased migratory and invasive potential. Such invasive phenotype is associated with hyperactivation of CXCR4 and FAK and their downstream AKT and ERK signaling pathways. Treatments with WZ811 and PF-573228 significantly reduced migratory and invasive capacity of NCI-H460-mt/mt and COR-L23 cells that was accompanied by the downregulation of AKT signaling. In addition, these two inhibitors showed trend to improve survival of SCID mice with orthotopically inoculated COR-L23 cells that extensively invaded lung parenchyma and developed distant metastases compared to NCI-H460 H460 derived tumor.

**Conclusions:** Overall, we demonstrated that p53/PTEN deficient NSCLCs have extremely invasive phenotype and provided a rationale for the use of CXCR4 or FAK inhibitors for the suppression of NSCLC dissemination.

**Legal entity responsible for the study:** This study was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia (Grant Nos III41031 and 173020), COST Action CM1106, “Chemical Approaches to Targeting Drug Resistance in Cancer Stem Cells” and COST Action CM1407, “Challenging organic syntheses inspired by nature - from natural products chemistry to drug discovery”.

**Funding:** This study was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia (Grant Nos III41031 and II540130).

**Disclosure:** All authors have declared no conflicts of interest.

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**1669P RalB GTPase: A potential novel target for RAS mutant colorectal cancer**

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**Background:** Colorectal cancer is the 3rd most common cancer in the UK, with around 40,000 new cases diagnosed annually. CRC patients have a 5-year overall survival rate of < 10% and more than 50% will die of metastatic disease. Intrinsic or acquired resistance to chemotherapeutic drugs is a major problem in CRC and developing an effective treatment strategy is therefore of the utmost importance. CRC cases harbouring RAS mutations (>50% cases) are associated with poor prognosis; this mutation has proven to be an important predictive factor for response to EGFR targeted therapies. Failure to target the RAS oncogene has resulted in a concentrated effort to discover targets within the downstream components of this pathway. In this study, we evaluate the roles of the small GTPases, RaLa and RalB, as novel targets in RAS mutant (MT) CRC. The RALGDS/RAL pathway constitutes a RAS effector pathway and mediates cell survival, proliferation and tumourigenesis. RalB in particular contributes to cell survival through TPK1 signaling.

**Methods:** We used an siRNA-based approach silencing RALB and RALB both individually and simultaneously in a panel of eight RAS-MT and RAS-WT cells with and without the addition of the MEK1 AZD6244 (Selumetinib). Knockdown efficiency and subsequent signalling events were assessed by western blotting. Flow cytometry and MTT assays were used to measure cell death and cell viability respectively. Connectivity mapping using data from microarray experiments was used to identify drugs mimicking the phenotype observed with siRALB, subsequently leading to the investigation of a TPK1 inhibitor which is currently ongoing.

**Results:** We found that silencing RALB, RALB both led to the greatest amount of cell death in RAS-MT but not WT CRC cells. In addition, a significant increase in cell death was observed when RALB silencing was combined with MEK inhibition. Cell death was found to be mediated by Caspase 8 and involved an upregulation of death receptor 5.
Pharmaceutical Company All other authors have declared no conflicts of interest. Funding: Janssen Pharmaceutical Company

Legal entity responsible for the study: Queen’s University Belfast
Funding: Queen’s University Belfast, Cancer Research UK
Disclosure: All authors have declared no conflicts of interest.

1670P
Serial genotypic characterization of circulating tumor cells (CTCs) in patients with metastatic castration resistant prostate cancer (mCRPC) undergoing treatment with abiraterone acetate (abi) or enzalutamide (enza)

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Background: While enza and abi have substantially improved outcomes for patients (pts) with mCRPC, de novo and acquired resistance mutations are increasingly recognized.

Methods: Pts receiving abi or enza in the course of routine clinical care were consented for blood collection at weeks 0, 4, 8, and 12 of therapy, and at the time of progression (based on Prostate Cancer Working Group 3 [PCWG3] criteria). CelIsaw was used for CTC enumeration; individual cells were isolated and subsequently classified for EpCAM and CD45 positivity. RNA sequencing (RNA-seq) was performed on pools of up to 10 CTCs.

Results: Amongst 36 pts enrolled, median age was 71 (range, 54–84) and median PSA was 21.9 ng/dL (range, 0–918.3). Regarding treatment, 21 pts received abi and 15 received enza. By PCWG3 criteria, 23 pts met the definition of progression on abi or enza. Mean/median CTC count was 158/6 (IQR 25%–75%, 0–15). On RNA-seq of CTCs collected at the time of progression, AR was the most mutated gene followed by ATRX, GNAS, FOXA1, KMT2A and CNOT1. Several deleterious mutations in the DNA damage response genes were noted including frameshift mutations in BRIDG, MSH2 and MLH1. Differential gene expression analysis between abi/enza sensitive and abi/enza resistant samples revealed 2100 differentially regulated genes in drug-resistant CTCs. Inhibition of Wnt signalling pathway analysis was used to identify pathways altered due to differential regulation of these genes. Among these pathways, TGFβ and CDDN1 signalling were found to be significantly up-regulated in drug resistant CTCs. In vitro enza-resistant models will be presented, offering validation of our clinical findings.

Conclusions: RNA-seq of CTCs representing abi/enza sensitive and resistant patients can identify potential mechanisms of resistance. Therapies targeting the downstream signalling mediated by CDDN1, such as CDK4/6 inhibitors (e.g., palbociclib or ribociclib), could avert resistance. Targeting TGFβ, another putative mediator of resistance, may be warranted.

Legal entity responsible for the study: Sumanta Kumar Pal
Funding: Janssen Pharmaceutical Company
Disclosure: J. Patel, B. Foulk, V. Bhargava, D.A. Smirnov: Working for Janssen Pharmaceutical Company All other authors have declared no conflicts of interest.

1671P
A novel circulating cell free DNA-based assay can predict tumor response to systematic chemotherapy

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Background: Although circulating cell-free DNA (cDNA) in blood is being touted as a frontier non-invasive approaches, its clinical utility still remains questionable. The purpose of this study was to compare the efficacy of cDNA by comparing with blood CEA levels and radiological evaluation in patients with unresectable metastatic colorectal cancer (mCRC) during treatment of systemic chemotherapy.

Methods: In this study, 12 patients with mCRC who were intended to receiving systemic chemotherapy were enrolled. Methylation status of CpG sites, considered as cancer-specific alteration, and concentration of cDNA were evaluated from blood plasma obtained before administration of systemic chemotherapy in each treatment cycle. To analyze aberrant cancer-specific methylation, we modified the highly sensitive assay for baselife DNA (Hi-SA) followed by fluorescence-based PCR, as reported previously (INCL 2009). Our modified methodology can detect 8 loci of target promoters, therefore methylation score (MS) could be ranged from 0 to 8 at a given time.

Results: Of the 12 patients enrolled, 10 patients experienced radiological progressive disease (PD). Plasma MS was significantly increased before radiological PD in 8 of 10 patients with PD. Thus MS had the median lead time of 73 days (range: 0-231 days) before documentation of radiological PD. In contrast, serum CEA level could predict PD only in the 2 patients before documentation of their radiological PD. Consequently, plasma MS could predict radiological PD with the median lead time of 9 days (range: 21 days) compared with serum CEA. We also examined whether cDNA concentration level in plasma was associated with radiological PD. Of the 12 patients, only 3 patients increased cDNA concentration level before radiological PD with the median lead time of 88 days (range: 21-140 days).

Conclusions: Our circulating cell free DNA-based assay is a robust methodology for capturing DNA methylation in circulating cell-free DNA in plasma, and is useful for the early identification of CRC patients that are at risk of developing PD prior to radiographic documentation.

Legal entity responsible for the study: Takashi Nagasaka
Funding: None
Disclosure: All authors have declared no conflicts of interest.

1672P
cDNA might expand therapeutic options for second line treatment of KRAS mutant mCRC

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Background: KRAS mutations predict failure of anti-EGFR therapies, thus genotyping colorectal cancer (CRC) is crucial for personalized treatments. Cancer heterogeneity hampers the assessment of KRAS mutational status in tumor tissues, leading to the search for alternative sources of cancer genetic information. cDNA of patients treated with anti-EGFR drugs exhibit pulsatile levels of KRAS mutations, revealing that the CRC genome adapts to EGFR inhibition by intertwinning EGFR blockade. These data support the use of liquid biopsy to monitor the molecular underpinnings of resistance to anti-EGFR agents. Research has been selectively concentrated on the emergence of resistant clones in the blood of patients with wtKRAS CRC as biomarker of anti-EGFR therapy resistance. Conversely our group demonstrated that patients with metastatic CRC harboring mutated primary tumors, thus not candidate to EGFR inhibitors, frequently have wtKRAS circulating tumor cells in blood. To explain the prevalence of wtKRAS clones in these patients, the generation of hypoxia has been suggested. We aimed to determine if anti-angiogenic drugs might drive the biological evolution of mKRAS clones towards a prevalent wtKRAS disease, by cDNA.

Methods: Ten patients with histologically confirmed mKRAS mCRC candidate to first-line anti-angiogenic drugs were prospectively enrolled. To investigate whether wtKRAS clones emerge as dominant under treatments, serial blood draws were performed at baseline and at 3 months of treatment. Idylla®(Biocrates) cKRAS Mutation Assay was used to track KRAS mutational status in serial cDNA determinations for each patient.

Results: At baseline, KRAS mutational status in cDNA was found concordant with tumor tissues in all patients analysed. At 3 months, 9/10 (90%) of mKRAS CRC patients treated with anti-angiogenic drugs switched to wtKRAS cDNA in peripheral blood.

Conclusions: These preliminary data suggest that patients with mKRAS colon cancer not infrequently switch to a prevalent wtKRAS disease in course of treatment with anti-angiogenic drugs. If confirmed in a large population, these results might shift second-line therapeutic options for KRAS mutant mCRC patients from insufficient to promising.

Legal entity responsible for the study: Paola Gazzania
Funding: Merck
Disclosure: All authors have declared no conflicts of interest.

1673P
Ex vivo expansion of circulating tumor cells for individualized drug susceptibility in patients with advanced or recurrent oesophageal cancer

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Background: Esophageal cancer (EC) is the eighth most common cancer in the world. The incident rate of EC is significantly high in Asian countries compared to rest of the world. Circulating tumor cells (CTCs) derived from EC have the potential to be precursors of metastasis. It is therefore of paramount interest to isolate and characterize CTCs from EC patients to monitor and detection of recurrence. The aim of present study is to evaluate drug response using patient-derived CTC cultures obtained from EC.

Methods: Custom microfabricated tapered microwells will be integrated with microfluidics to expand CTC clusters without any prior enrichment. The established CTC cluster assay will be used to screen anticancer drugs. The drug concentrations selected will be centered on the IC50 that had previously established for each drug across EC cell lines. Cluster formation in culture will be correlated with overall patient survival. 50 patients with a proven diagnosis of EC attending the Department of Surgical Oncology, Kidwai Institute of Oncology will be enrolled into the study.
Results: Our initial results showed CTC clusters formation in the patients with metastatic EC. This cluster formation was affected by the presence and duration of systemic therapy. We observed a progressive reduction in cluster formation in samples from patients who had undergone increasing longer treatment.

Conclusions: Our result suggests that CTC cluster can be used to rapid evaluation of drug response. We would further use the CTC cluster assay as a potential tool for evaluating patient prognosis during treatment. The study will be employed to determine the drug susceptibility pattern in individual patients and also provide therapeutic choices for personalized treatment.

Legal entity responsible for the study: Kidwai Memorial Institute of Oncology.

Funding: Department of Science and Technology, (DST) Government of India.

Disclosure: All authors have declared no conflicts of interest.

1674P Exploratory study of CK-M30 and pHH3 expression in Circulating Tumor Cells (CTC) as biomarkers of docetaxel (DOC) efficacy in metastatic castration resistant prostate cancer (mCRPC)

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Background: A drop in CTC counts as early as 4 weeks following treatment initiation have been suggested as an indicator of overall survival (OS) benefit. DOC remains a pivotal treatment in mCRPC for which there are no early pharmacodynamic (PD) markers of response to DOC treatment.

Methods: We conducted a prospective 2-cohort multicenter exploratory study in mCRPC pts receiving DOC. We measured markers of apoptosis (CK-M30) or mitosis arrest (pHH3) in mCRPC pts receiving DOC.

Results: Variability of DOC. Biomarker results are summarised in Table.

Conclusions: Our result suggests that CTC cluster can be used to rapid evaluation of drug response. We would further use the CTC cluster assay as a potential tool for evaluating patient prognosis during treatment. The study will be employed to determine the drug susceptibility pattern in individual patients and also provide therapeutic choices for personalized treatment.

Legal entity responsible for the study: Kidwai Memorial Institute of Oncology.

Funding: Department of Science and Technology, (DST) Government of India.

Disclosure: All authors have declared no conflicts of interest.

Table: 1674P Variability

<table>
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<tr>
<th></th>
<th>Basal 1 (N = 60) Median (Range)</th>
<th>Basal 2 (N = 57) Median (Range)</th>
<th>%marker Corr. Coeff</th>
<th>Post-24h (n = 59) median (Range)</th>
<th>P-value Basal vs post-24h</th>
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<tr>
<td><strong>Cohort CK-M30</strong></td>
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<td>CTC/7.5mL</td>
<td>9 (5-1266)</td>
<td>8 (5-863)</td>
<td>0.54 p = 0.763</td>
<td>9 (4-1129)</td>
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<td>CK-M30+</td>
<td>48% (0-76%)</td>
<td>35% (0-100%)</td>
<td>0.05 p &lt; 0.001</td>
<td>9 (3-584)</td>
<td>&lt;0.001</td>
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<tr>
<td>pHH3</td>
<td>10 (5-567)</td>
<td>12 (4-623)</td>
<td>0.05 p &lt; 0.001</td>
<td>9 (3-584)</td>
<td>&lt;0.001</td>
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<tr>
<td>response factor</td>
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<td>p-value</td>
<td>OS median (C19%)</td>
<td>p-value</td>
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<tr>
<td><strong>Conclusion</strong></td>
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<tr>
<td><strong>CK-M30+ change 24h</strong></td>
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<tr>
<td>CTKM30 + &gt;50%</td>
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<td>11</td>
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1675P Risk of recurrence prediction and optimum treatment planning for early stage breast cancer patients: A cost-effective, accurate and broad based solution for Asia

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Background: Current molecular risk stratification tests have helped clinicians to optimize Chemotherapy for early stage breast cancer patients leading to huge savings in treatment costs and improved quality of life. However, current tests are not impactful in the Asia due to the extreme cost-sensitivity of the market. Aim of this study was to develop and validate a cost-effective, broad based and robust test to stratify early stage hormone receptor positive patients based on individual risk of recurrence.

Methods: A retrospective cohort of 300 patients, was used to develop ‘CanAssist-Breast’, a Morphometric Immunohistochemistry based test comprising 5 biomarkers plus three clinical parameters (Tumor size, node status and grade) using SVM based algorithm. CanAssist-Breast biomarkers belong to key signaling pathways involved tumor invasion and chemotherapy resistance.

Results: CanAssist-Breast classifies patients into ‘low or high’ risk of recurrence based on ‘CanAssist-Breast Score’ score. Test validation in a 800+ sample cohort demonstrated that it is useful in both node negative and positive patients, as well as chemotherapy naive and treated patients. CanAssist-Breast Score, is a strong independent predictor of disease recurrence by multivariate analysis. The majority of patients in ‘low risk’ had Stage 2, Grade 2-3 disease over Stage 1, Grade 1 disease. Comparison with commonly used prognostic tools including Ki67, the online tool PREDICT and Oncootype DS showed that CanAssist-Breast test was superior in determining prognosis.

Conclusions: CanAssist-Breast is a low-cost, prognostic and chemotherapy predictive test to predict risk of recurrence and enable optimal treatment planning in patients with early stage Breast Cancer in Asia.

Legal entity responsible for the study: DCGI registered Ethical Committee based in Bangalore, India.

Funding: Onco Stem Diagnostics Private Limited

Disclosure: M.M. Bakre, Onco Stem Diagnostics is start-up biotechnology company privately funded by venture capitalist. The retrospective, non-interventional, observational study was approved by DCGI registered Ethical Committee based in Bangalore, India. All other authors have declared no conflicts of interest.

1676P Comparison of progression-free survival (PFS) on comprehensive multiparameter profiling-guided therapy to PFS on prior therapy: A pooled analysis from 4 contemporary prospective studies

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Background: It is expected that the progression-free survival (PFS) for patients with refractory cancers will decline over subsequent lines of therapy. Patients with refractory metastatic cancer have previously been shown to derive some clinical benefit from comprehensive multiparameter profiling (CMP) of tumor tissue. Data from four...


1677P

Effect of enoxaparin, omeprazole, gencitabine and bortezomib in refractory patients
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Background: Repurposing drugs and immunogenic chemotherapy for cancer is an emerging field, especially the combination of drugs with validated data. Several studies have shown that enoxaparin, omeprazole, gencitabine and bortezomib have immunomodulatory properties that synergize with several chemotherapeutic protocols and decrease chemoresistance in several tumors. We treated refractory patients with ECOG=0 with this combination. We demonstrated significant clinical response that correlated with the immune response after 2 months of weekly treatment.

Methods: GCIS IRB approved this protocol and informed consent was signed. We included 10 patients, median age 45 years old of each tumor with at least 2-4 relapses. The patients receive intravenous 0.5 gr/m2 of gemcitabine, 3.5 mg of bortezomib, 80 mg of omeprazole and enoxaparin was administrated subcutaneously in the area where the patients received targeted therapies, either alone or in combination with chemotherapy or hormone therapy.

Results: Contrary to the expected decline in PFS, patients had a better outcome when treated with CPM-guided treatments. This was interestingly driven by the precision use of available chemotherapeutic resources rather than sometimes inaccessible targeted therapies. Further prospective trials in specific tumor types may help to highlight particular patient populations who might benefit most from CPM guidance.

Legal entity responsible for the study: Gunther Gastl
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All other authors have declared no conflicts of interest.

1678P

A new chemotherapy-based combination to prevent osteosarcoma progression
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Background: Despite the intensification of chemotherapy regimen, 5 years survival rates for patients with metastatic or relapsed osteosarcoma (OS) remains of 20%. The secreted factor netrin 1 (Nt1) is overexpressed in many human cancers to block apoptosis. Recent studies showed that blocking Nt1 interaction with its receptors potentiates chemotherapy efficacy suggesting that combining chemotherapies with Nt1 interference could be a promising approach for chemoresistant tumors like OS.

Methods: Analyses of the ATG_Sarc database (http://atg-sarc.sarcomabcb.org/), indicate that Sarcoma with complex genomic (SCG) with a higher expression of Nt1 have a poorer outcome (p < 0.002). In addition, qPCR performed on human sarcoma samples showed that Nt1 is higher expressed in OS compared to other SCG (7.75 fold increase – p < 0.002). Those data indicated that Nt1 could be a potential target for OS treatment. Thus, we evaluated the antitumoral effects of anti Nt1 monoclonal antibody (aNt1) combined to doxorubicin (Dox) in a rat syngeneic and metastatic OS model. In this model, treatments were administered either on progressive OS or post operatively to prevent OS relapse. At the end of the experiments tumors and lung were collected for IHC analyses.

Results: As pre operative treatment, Dox/aNt1 combination caused a marked delay in OS progression (median end point reached at day 17 and day 22 respectively in Dox and Dox/aNt1 group, <p < 0.02) and dramatically slowed down metastatic spreading: lung metastases (d < 5mm) were found respectively in 75% and 17% of Dox and Dox/aNt1 treated rats At post operative treatment, Dox/aNt1 combination significantly increased animals survival (median end point reached at day 15 and day 21 respectively in Dox and Dox/aNt1 group, <p < 0.02). Moreover, 19 days after tumor resection, 10% of the Dox treated tumors had r1 relapsed versus 40% in the Dox/aNt1 treated group. A variation in tumor vascular density caused by the treatment was found in the Ant Nt1 treated groups as shown by IHC experiments tumors and lung were collected for IHC analyses.

Conclusions: Our study reporting the antiangiogenic and antitumoral effects of Dox/aNt1 Combination in OS indicate that this combined treatment could be a way to overcome OS chemoresistance.

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1679P

Mutant KIT translocates into the nucleus and induces NFKBIB expression that leads to KIT expression in imatinib-resistant gastrointestinal stromal tumors
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Background: Gastrointestinal stromal tumor (GIST) is a dominantly mutant KIT-driven tumor. Prolonged tyrosine kinase inhibitor (TKI) treatment may result in a resistant phenotype through acquired secondary KIT mutation. Increasing evidences show that membrane-bound receptors, as EGFR, can translocate into the nucleus, mediate genes expression, and lead to tumor survival and drug resistance. However, it’s barely known the nuclear role of KIT in GIST.

Methods: In this study, two imatinib (IM)-resistant GIST cell lines, GIST48 and GIST430, were used as a model.

Results: In this study, we first showed that KIT is distributed both in the cytoplasm and the nucleus in IM-resistant GIST cells. Using ChIP-seq and CHIP assay, we identified that nuclear KIT bound to the NFKBIB promoter region and regulated its expression. The expression levels of NFKBIB and phospho-KIT were significantly correlated with NCCN-risk category in surgically resected GISTs stained by immunohistochemistry. The cell viabilities were inhibited as accompanying with KIT reduction in GIST cells while NFKBIB was silenced or RELA was overexpressed. Moreover, RELA was activated, translocated into the nucleus, and bound to KIT promoter region in NFKBIB-silenced or RELA-overexpressed GIST cells. Valproic acid, acted as a NFκB inducer, could induce RELA nucleus translocation and binding to KIT promoter region that led to the reduction of protein and RNA expression level of KIT and the cell viabilities of GIST cells. Furthermore, the combination of IM with low dose valproic acid showed synergistically inhibitory effect on cell viabilities of GIST cells and comparable effects on reducing phospho-KIT level and inhibiting tumor growth as high-dose valproic acid did in GIST430 xenograft models.

Conclusions: Taken together, we first demonstrated that phosphorylated KIT could translocate into the nucleus and drive itself expression in IM-resistant GIST cells through mediating NFKBIB expression. In addition, our findings identified a novel and druggable KIT-NFKBIB-NFKB regulatory axis that provides a new insight on tumorigenesis and therapeutic option for IM-resistant, mutant KIT-expressing GISTs.

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1680P Reversion of epithelial–mesenchymal transition (EMT) as a mechanism of action of cabazitaxel in castration-resistant prostate cancer

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Legal entity responsible for the study: patients progressing to prior therapies in CPRC.

The reversion of EMT phenotype, trough induction of SCD-1 and CDH1, has been shown to be associated with acquisition of drug resistance. Prolonged survival of P100v tumor-bearing mice was observed when these tumors were treated with bortezomib-resistant RPMI 8226 (P100v) cell line as projected via QPOP, with these drug combinations as first and secondary lines of treatment. The inclusion of pro-tein turnover inhibitors, such as bortezomib, into these drug combination regimens has been shown to diminish tumor growth in vivo, pointing at this complex as a novel target for cancer therapy.

Results: Microarray data, pathway analysis and EMT gene data in in vivo validation showed that EMT occurred in both D-R and CZ-R cell lines, being ZEB1 one of the top deregulated genes. However, we identified 55 EMT genes differentially deregulated between D-R and CZ-R parental cells. Among them CDH1, and ESRRB (lost in D-R but maintained in CZ-R), and AXL (deregulated in D-R and downregulated in CZ-R). D-R cells presented a more pronounced mesenchymal phenotype (morphology, higher migration and proliferation rates, higher expression of EMT markers in mRNA and protein level) than CZ-R. Dose-response experiments showed that CZ induced CDH1 and ESRRB expression in different cell lines. ZEB1 inhibition reverted D- resistance, but not CZ-R, and restored ESRRB expression in D-R cells. In 29 CRPC patients treated with CZ, low level of expression of ESRRB 1 in tumor correlated with a better PSA-PFS (6.2 vs 2.7 months, P = 0.006; HR: 0.31 P = 0.009) and radiological PFS (7.9 vs 3.3 months, P = 0.047; HR: 0.39 P = 0.055) and the EMT phenotype was not associated to resistance.

Conclusions: The reversion of EMT phenotype, trough induction of CDH1 and ESRRB, may be a novel mechanism of action of CZ, which may explain its activity in patients progressing to prior therapies in CPRC.

Legal entity responsible for the study: Hospital Clinic of Barcelona

Funding: Sanofi-Aventis

Disclosure: All authors have declared no conflicts of interest.

1681P Globally optimizing therapeutic combinations against bortezomib-resistant multiple myeloma using a quantitative parabolic optimization platform (QPOP)

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Background: The compartmental activities of the pyruvate dehydrogenase complex sustain lipogenesis in prostate cancer. Hence, we asked whether these compartmental activities are also involved in prostate cancer progression.

Methods: We have developed the quantitative parabolic optimization platform (QPOP) to optimize drug combinations against bortezomib-resistant multiple myeloma. By mapping phenotypic output data to parabolic response surfaces, QPOP is able to deterministically optimize drug combinations as well as drug dosages.

Results: We have successfully identified potential optimal drug combinations against bortezomib-resistant RPMI 8226 (P100v) cell line as projected via QPOP, with these drug combinations as first and secondary lines of treatment. The inclusion of protein turnover inhibitors, such as bortezomib, into these drug combination regimens has been shown to diminish tumor growth in vivo, pointing at this complex as a novel target for cancer therapy.

Conclusions: Taken together, our findings demonstrate that mitochondrial and nuclear PDC sustains prostate tumourigenesis by controlling lipid biosynthesis thereby pointing at this complex as a novel target for cancer therapy.

Legal entity responsible for the study: Molecular Oncology, Institute of Oncology Research

Funding: IBBA Foundation

Disclosure: All authors have declared no conflicts of interest.

1683P Metabolomics in cancer cachexia

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Background: Cancer cachexia is a frequent unmet medical need. CC affects up to 80% of cancer patients, and it is indirectly responsible for at least 20% of cancer deaths. The pathophysiology is characterized by a variable combination of reduced food intake and abnormal metabolism, including systemic inflammation and negative protein and energy balance. Despite its high clinical significance, definite diagnostic criteria of cachexia are lacking. The ‘omics’ technologies provide a global view of biological systems. Among these, blood-based metabolomics is a promising method for cachexia study.

Methods: This study is part of a pilot, observational, cross-sectional, case-control, cross-sectional, case-control, cross-sectional, case-control, cross-sectional, case-control, cross-sectional, case-control, cross-sectional, case-control, cross-sectional, case-control, cross-sectional, case-control, cross-sectional, case-control, cross-sectional, case-control, cross-sectional, case-control, cross-sectional, case-control, cross-sectional, case-control, cross-sectional, case-control, cross-sectional, case-control, cross-sectional, case-control, cross-sectional, case-control, cross-sectional, case-control, cross-sectional, case-control, cross-sectional, case-control, cross-sectional, case-control, cross-sectional, case-control, cross-sectional, case-control, cross-sectional, case-control, cross-sectional, case-control, cross-sectional, case-control, cross-sectional, case-control, cross-sectional, case-control, cross-sectional, case-control, cross-sectional, case-control, 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and multivariate methods, using principal component analyses and error adjustments for multiple comparisons.

Results: from metabolomics study are shown. Subjects: 15 cancer (ca) patients (pts), distributed as follows: Cachexia (C): 8 pts (male:female 7:1; pancreatic ca: 3, mela-

notons 4.5). Results: DII has an impact on levels of urinary enterolignans when enterolignans were dichotomized at the 90th percentile value. In this same sample, the greatest affected group of Mbl was ‘amino acids and derivatives’, all decreased. Glycophospholipids, sphingolipids, steroid

dietary inflammatory indexTM (DII) has an impact on levels of urinary enterolignans in the National Health and Nutrition Examination Survey (NHANES) 2003-2008. We also carried out validation of the DII with C-reactive protein (CRP).

Methods: Data came from NHANES 2003-2008. Enterolignans (enterodiol and enterolactone) and CRP were assayed from urine and serum specimens, respectively. DII

Results: After adjustment, higher DII scores (i.e., relatively more pro inflammatory) were associated with lower levels of creatinine normalized enterodiol (bDIIquartile4vs1

Conclusions: These finding suggest that plasma amino acids and lipids profiling has great potential for improving cachexia screening, and to understand disease pathogenesis. Of note, the increased values of cortisol should lead us to revisit the use of glucocorticoids in this setting. Subtractive therapy for some of the observed deficiencies might deserve clinical exploration.

Legal entity responsible for the study: Instituto de Investigación Sanitaria Hospital 12 de Octubre

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1684P

Association between the Dietary Inflammatory Index (DII), urinary enterolignans and C-reactive protein in the National Health and Nutrition Examination Survey-2003-2008

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Background: Enterolignans are important biomarkers of microbiome diversity. Higher levels of enterolignans have been shown to reduce cancer risk. Diet and inflammation have been shown to play a role in maintaining microbiome diversity. This study examined whether inflammatory potential of diet, as measured by the Dietary Inflammatory IndexTM (DII) has an impact on levels of urinary enterolignans in the National Health and Nutrition Examination Survey (NHANES) 2003-2008. We

and multivariate methods, using principal component analyses and error adjustments for multiple comparisons.

Results: from metabolomics study are shown. Subjects: 15 cancer (ca) patients (pts), distributed as follows: Cachexia (C): 8 pts (male:female 7:1; pancreatic ca: 3, melano-

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Results: After adjustment, higher DII scores (i.e., relatively more pro inflammatory) were associated with lower levels of creatinine normalized enterodiol (bDIIquartile4vs1

Conclusions: These finding suggest that plasma amino acids and lipids profiling has great potential for improving cachexia screening, and to understand disease pathogenesis. Of note, the increased values of cortisol should lead us to revisit the use of glucocorticoids in this setting. Subtractive therapy for some of the observed deficiencies might deserve clinical exploration.

Legal entity responsible for the study: Instituto de Investigación Sanitaria Hospital 12 de Octubre

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1685P

Fullerol/iron nanocomposite modulates doxorubicin-induced cardiotoxicity

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Background: Doxorubicin is a first line cancer chemotherapy. Unfortunately, its clinical use is limited by its cardiotoxicity. It is known that iron overload aggravates anthracytotoxicity. Fullerol is a 1 nm size molecule and in aqueous solutions is in the form of polymeric nanoparticles, which enables them to serve as a good carrier of positively charged ions such as Fe3+. Fullerol’s antioxidant activity through scaveng-

The aim of our study was to investigate the effects of the fullerol/iron nanocomposite as a pretreatment to doxorubicin on the rat’s heart in comparison to doxorubicin alone. After the 24h-treatment, adult male Wistar rats were sacrificed and hearts were collected for ultrastructural and qRT-PCR analyses. To test the ability of doxorubicin to induce oxidative stress, and the fullerol’s capability to mitigate it, we had chosen to monitor gene expression of enzymes involved in antioxidant defense.

Results: Ultrastructural study revealed that in the group pretreated with the nanocom-

posite prior to doxorubicin application cardiomyocytes were with preserved morphol-

ogy and the structure of intercalated discs. On the other hand, the heart tissues of animals treated with doxorubicin alone were significantly more damaged. Intensive interstitial vacuolization was observed, as well as vacuolization of cardiomyocytes, hypercon-

traction of sarcomeres, mitocondria of irregular shapes. qRT-PCR results have shown that neither treatment with doxorubicin alone nor the pretreatment with the nanocom-

posite did cause significant increase in mRNA levels of catalase and superoxide dismutase.

Conclusions: Our results indicate that the fullerol/iron nanocomposite applied as pretreatment to doxorubicin induces less damage to the heart tissue in comparison to doxorubicin alone.

Legal entity responsible for the study: Aleksandar Dijordevic

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Disclosure: All authors have declared no conflicts of interest.

1686P

Ability of TMRSS2-ERG (TE) expression to predict taxane benefit depending on prior abiraterone or enzalutamide therapy in castration-resistant prostate cancer


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Background: TMRSS2-ERG (TE) results in androgen-driven overexpression of ERG, which is involved in resistance to taxanes in preclinical models. In prior work we showed that TE expression in blood correlated with taxanes resistance in metastatic castration-resistant prostate cancer (mcPCa). Here, we studied if the detection of TE in primary tumors predicts taxanes activity in CPCR. We also explored the impact of prior abiraterone or enzalutamide (A/E) in blood TE detection and in TE predictive value.

Methods: mcPCa patients (pts) treated with taxanes in a multicenter biomarker study were included. Formalin-fixed paraffin-embedded (FFPE) tumors and peripheral blood mononuclear cells (PBMCs) were tested for TE presence by RT-qPCR. FFPE were retrospectively obtained. PBMCs were prospectively collected prior to taxane initiation. PSA-PFS was evaluated by Kaplan-Meier analysis using log-rank test. Univariate analysis of TE-status (+ vs -) was performed with Cox regression.

Results: 124 pts were included: 111 (89.5%) received docetaxel ( Dx, 13 (10.5%) caba-

zitaxel (Cz) and 27 (21.8%) both. Fifty-seven (45.9%) tumors were P in 13.6 months; HR 1.7, p < 0.05). No differences were observed in Dx treated pts with prior A/E (N = 31, 27.9%) according to tumor TE expression. In 44 pts, matched tumor and PBMC samples were available. Concordance between tumor an blood was 92.8% and 63.3% for pts with and without prior A/E, respectively. TE in blood was in 1 in (7%) pts with prior A/E and in 7 (23.3%) pts without prior A/E. As observed in FFPE samples, in patients without prior A/E to Dx (N = 28, 63.6%), blood TE correlated with lower PSA response (9% vs 61.9%, p < 0.01) and reduced median PSA-PFS (3.34 vs 8.2 mM, HR 4.1 p < 0.01).

Conclusions: The predictive value of TE in taxane resistance may be different depending on prior exposure to A/E. This is being tested in a multicenter prospective study.

Legal entity responsible for the study: Hospital Clinic de Barcelona/Institut d’Investigacions Biomèdiques Agustí Pi i Sunyer

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Disclosure: A. González del Alba: Advisory boards: Sanofi, Janssen, Astellas, Bayer. Travel expenses: Astellas, Sanofi, Janssen. All other authors have declared no conflicts of interest.

Identification of patient population with longer survival when treated with 5-1 plus cisplatin via predictive enrichment strategy analysis of the FLAGS and DIGEST phase III trial

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Background: The FLAGS trial, a randomized phase III trial, compared 8:1, an oral fluoropyrimidine plus cisplatin (SP) with 5-fluorouracil plus cisplatin (FP) in the first-line treatment for advanced gastric cancer (AGC). The results led to the approval of SP by EMA, and it is now marketed in Europe. The purpose of this analysis was to establish a clinical covariate(s) model using the Predictive Enrichment Strategy Analysis (PESA) identifying patients who benefit from SP.

Methods: PESA is a new robust methodology with guidelines by the United States Food and Drug Administration. Consensus-based 15 clinical covariates were selected for PESA and a large cohort with no missing data (FLAGS trial: 889 patients) was analyzed. The models generated were cross-validated and the results analyzed were validated in the DIGEST trial, a phase III trial comparing SP to FP in diffuse type advanced gastric cancer. From the DIGEST trial, 333 patients and 14 clinical covariates were used in the analysis.

Results: In FLAGS, ECOG Performance status (PS = 1) was the strongest covariate in the enrichment group showing benefit for SP. In the population with PS = 1, the OS in the SP group was significantly longer than the FP group (Hazard Ratio [HR] = 0.798, 95%CI = 0.66-0.96; p = 0.0166). Other covariates with high potential to be associated with SP benefit included: diffuse-type histology, positive peritoneal metastases, and the lack of liver metastases. In DIGEST PS = 1 also showed: HOS most associated with SP benefit. While there was no strong signal from the variables positive peritoneal metastases, and the lack of liver metastases, there appeared to be a signal from the neutrophil variable. In the DIGEST population of diffuse type, patients with PS = 1 and low baseline neutrophil count may benefit from SP.

Conclusions: Presence of PS = 1 was associated with SP benefit in both the FLAGS and DIGEST trial. Although peritoneal and liver metastases resulted in slightly different signals in the trials, further analyses will be done to look at the impact of low baseline neutrophil count on the benefit of SP for PS = 1 and diffuse type histology patients.


Legal entity responsible for the study: Taiho Pharmaceutical Co., Ltd.

Funding: Taiho Pharmaceutical Co., Ltd.


HMGA1 is a new biomarker of liposarcoma progression

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Background: Liposarcoma (LPS) is the most common type of soft-tissue sarcoma that includes a heterogeneous class of tumors classified according to histologic appearances, protein expression pattern and molecular subtypes being not only important but may be necessary as a basis for the identification of therapeutic targets. Lipoma is characterized by extensive High Mobility Group A1 (HMGA1) protein aberrations suggesting a role of this protein in the mechanisms of liposarcoma progression as well as previously described in other tumors.

Methods: Cell lines derived from different liposarcoma subtypes and a cohort of 68 patients were used to analyze in vitro and in vivo the role of HMGA1 in liposarcoma progression.

Results: Our data revealed that HMGA1 is highly expressed in liposarcoma cell lines and that is strongly involved in the mechanism of cell proliferation, mobility and invasion of this subtype of tumor. The in vitro results were confirmed in vivo by the RT-PCR and IHC analyses of 68 specimens of different subtypes of liposarcoma derived from patients surgically treated at Regina Elena National Cancer Institute. The aggressive subtypes de-differentiated and myxoid liposarcoma showed higher HMGA1 levels than well-differentiated liposarcoma. Furthermore, trabeculization, a marine alkaloid isolated from the tunicate Ecteinascidia turbinata, down-regulates HMGA1 and E2F1, as well as its downstream targets Vimentin and ZEB1 in sensitive myxoid liposarcoma cells, suggesting a critical role of the transcriptional complex HMGA1/E2F1 in the regulation of the mesenchymal compartment. These data were further confirmed in vivo by the IHC analysis of myxoid sarcoma specimens derived from patients that received trabeculatin therapy before surgery. On the other hand, trabeculatin treatment down-regulates the activity of HER3 receptor that in turn inhibits NF-κB pathway in sensitive myxoid liposarcoma cells but not in resistant counterpart cells demonstrating that the activation of NF-κB pathway is involved in the mechanisms of drug resistance.

Conclusions: Overall, our data suggest that HMGA1 may represent a new biomarker of liposarcoma progression and that it could be a new potential therapeutic target for the more aggressive liposarcoma subtypes.

Legal entity responsible for the study: Regina Elena National Cancer Institute

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Analysis of DPYD and UGT1A1 genotype in patients with advanced pancreatic cancer treated with modified FOLFIRINOX

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Background: Modified FOLFIRINOX (mFOLFIRINOX) is a standard treatment in advanced pancreatic cancer (aPC). Because of the presence of either loss-of-function mutations in DPYD (c.1697> G, c.1794> A) and UGT1A1*28 variant associated with reduced UGT1A1 expression, deficiency of DPYD and UGT may result in drug accumulation and severe toxicities caused by fluoropyrimidines and ironotocan, respectively.

Methods: The present study analyses the association between DPYD and UGT variants and adverse drug reactions (ADRs) in aPC patients (pts) treated with mFOLFIRINOX. Blood samples were collected from 104 pts, and analyses of DPYD c.1697> G, c.1794> A and UGT1A1*28 were performed by automatic statistical analysis. Singularity was performed by chi-square, Mann-Whitney and Spearman’s rho tests on SPSS v.23.
Results: None of the pts was carrier of the c.1679G>c and c.2846T>alleles. Only one IVS14 > 1GA was found and 8 pts had c.2194AG genotype. ADRs grade (G) ≥3 were neutropenia (42.3%), diarrhea (7.9%) and stomatitis (7.9%). The statistical analysis of the IVS14 > 1GA has not been performed due to the extremely low frequency of the mutant allele (0.96%). However IVS14 > 1GA patient experienced G4 hematological and gastrointestinal ADRs after the first cycle. We observed a trend toward significant association between c.2194AG genotype and the risk of thrombocytopenia (p = 0.080) and hand-foot syndrome (HFS) (p = 0.096). The frequency of UGT1A1*28 allele was found to be 56% (54.4%) pts (1*/1*28, n= 38; *28/*28, n = 18) and it was correlated with the risk of developing thrombocytopenia (p = 0.006) and neutropenia (p = 0.044). Moreover, this risk increased as the number of *28 alleles increased (2*28 > 1*/1*28 > 1*/1*28, p = 0.005). No significant correlation with diarrhea was found.

Conclusions: Our data confirm that DPDP IVS14 > 1A is associated with life-threatening toxicities and that the c.2194A allele could be possibly associated with thrombocytopenia and HFS, but validation in a larger cohort is needed. UGT1A1*28 allele is associated with a higher risk of G3/4 thrombocytopenia and neutropenia, and should be implemented in routine practice to personalize treatment in aPCT.

Legal entity responsible for the study: University of Pisa

Funding: Institutional fundings

Disclosure: All authors have declared no conflicts of interest.

1693P Development of TP53 signature diagnostic system using multiplex RT-PCR and observational study to confirm the prognostic value of TP53 signature in breast cancer

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Background: Development of TP53 signature diagnostic system using multiplex RT-PCR and confirm the prognostic value of TP53 signature in breast cancer

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Methods: We made the multiplex RT-PCR system consists of 26 genes, 23 genes from the TP53 predictive genes and 3 internal control genes. TP53 signature status was determined by the ratio of expression levels of 16 genes that were upregulated in tumors with TP53 mutation to the sum of expression values of 7 genes downregulated in tumors with TP53 mutation. Cut-off value was set at 1.1 to maximize the sensitivity to detect the TP53 mutant signature. Using a 217 breast cancer case cohort, which was prospectively collected from 2007 to 2016, the relationship between the TP53 signature status and clinicopathological features and TP53 structural mutations were analyzed. And we validated the prognostic value of TP53 signature in 191 stage I-II patients.

Results: Of 217 patients, 102 patients were assigned to the TP53 mutant signature TP53 structural mutation was observed in 35.1% of patients with TP53 mutant signature and 6.9% of patients with TP53 wild-type signature. In 191 stage I-II patients, RFS of the patients with TP53 mutant signature showed significantly shorter than the patients with wild-type signature. Similar results were observed in 164 ER positive patients. In both univariate and multivariate analyses, TP53 signature status showed independent and better correlation to RFS than tumor size, LN status, stage, ER status and TP53 structural mutation status in stage I-II patients.

Conclusions: We developed the diagnostic system to determine TP53 signature status using multiplex RT-PCR. The TP53 status diagnosed by this system could be one of the prognostic biomarker of breast cancer.

Clinical trial identification: UMIN000005172

Legal entity responsible for the study: Ethics Committee at the Tohoku University Hospital.


Disclosure: All authors have declared no conflicts of interest.

1694P Expression of estrogen receptors and beta-III tubulin in non-small cell lung cancer tissue

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Background: Estrogen receptors beta (ERβ) are highly expressed in different normal and neoplastic tissues that, until recently, has been considered to be ER-negative based on ER expression evaluation. Among the genes, regulated via estrogen signaling there was one, coding microtubule protein beta-III tubulin (TUBB3). TUBB3 expression is found in many solid tumors and is linked to poor prognosis and resistance to taxanes. Since it is little known about mechanisms behind TUBB3 expression in non-small cell lung cancer (NSCLC), we decided to find out if there is a correlation between ER and TUBB3 expression in this type of cancer.

Methods: 104 surgical samples of NSCLC were converted to single-cell suspension, stained with primary anti-ERβ (ab1046), anti-ERβ (ab14104C), anti-TUBB3 (ab7751) antibodies and secondary fluorescent antibodies. Immunofluorescent estimation was performed using flow cytometry. Expression level was determined as the ratio (%) of specifically fluorescent cells to the number of cells stained with secondary antibodies. Spearman rank correlation was used to test the association between variables.

Results: Both ER were revealed in all NSCLC specimens. Mean expression level of ERβ was significantly higher compared with ERα (46.6 ± 17.0% vs 23.2 ± 14.2%, respectively). Mean TUBB3 expression level was 43.1 ± 15.7%. In all the tumors investigated only weak correlation observed between ER status and TUBB3 expression level (r = 0.3 and r = 0.4 for ERα and ERβ, respectively). In the group of squamous cell cancer specimens (n = 68) the association was strong (r = 0.5 and r = 0.5 for ERα and ERβ, respectively). In the group of adenocarcinoma specimens (n = 36) the correlation between ERα and TUBB3 was very weak (r = 0.3) and there was no correlation between ERβ and TUBB3.

Conclusions: 1. Strong correlation between TUBB3 and ER expression was found only in squamous cell cancer tissue. 2. The dominant type of estrogen receptors is ERβ. 3. In clinical terms high ERβ expression means that in case of resistance to standart plati-num/taxane duplets, patients with high tumor ERβ expression may benefit from anis-trogyn therapy: Supported by RFBR grants (N N15-04-01891-a, 16-34-01049-mol-a) and grant of the President of RF MK-7709.2016.7.

Legal entity responsible for the study: N.N. Blokhin Russian Cancer Research Center.
1695P Deciphering the antitumor efficacy and mechanistic delineation of epigenetic inhibitors in AML using patient tumor derived ex vivo phenotypic assay based platform

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Background: Epigenetic inhibitors have demonstrated tumor suppression efficacy by modulating genes involved in growth, proliferation, and invasiveness in hematological malignancies like AML. Preclinical evidences suggest therapeutic benefit by combining epigenetic drugs along with other therapeutics like JAK2 inhibitors. However, there is a huge unmet need to understand the disparities in response at the individual patient level.

Methods: We developed a novel functional assay based platform called CANscriptTM to predict the efficacy of anticancer drugs in clinic, which mimics patient tumor microenvironment (Majumder B et al., Nature Communications, 2015). Utilizing samples from AML patients we interrogated response to HDAC and DNA MTase inhibitors by assessing tumor viability, proliferation, morpholgy, and death in this platform. To elucidate the mechanisms of our response, we delineated the pharmacodynamic and pathway moduation by immunohistochemistry and mRNA microarray.

Results: Thirty-two AML patients samples were analyzed in this platform. HDAC and DNA MTase blockaded resulted antitumor response, which was demonstrated by differential and functionally distinct patterns of target engagement. mRNAs and pathway specific protein expression profiling is suggestive of JAK2 pathway deregulation in many of the non-responders. Treatment with JAK2 inhibitor in this cohort led to efficacy in 40% of these non-responders, suggesting the critical role of this pathway. Interestingly, unique JAK2 signatures associated with single agent vs. combination therapy was observed (18%), hinting at functionally distinct mechanisms of antitumor effects at individualized levels.

Conclusions: These findings demonstrate the utility of this ex vivo platform to predict therapeutic response of epigenetic modulators at the individual patient tumor. It also highlights that, within a contextually heterogeneous framework, distinct mechanisms orchestrate response to HDAC and DNA MTase inhibitors as a single agent or in combination with JAK2 inhibitors. Insights gained from these findings can re-shape our strategic thinking of drug selection for the treatment of AML.

Legal entity responsible for the study: Mitra RxDx

Funding: Mitra RxDx

Disclosure: G. Babu: Independent consultant and full time employee of Kidwai Memorial Institute of Oncology, scientific and clinical advisory board of Mitra Biotech and equity in this organization. All other authors have declared no conflicts of interest.

1696P Proteomics of triple negative breast cancer developing metastases to central nervous system


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Background: Breast cancer (BC) is the most frequent tumor in woman, representing 20-30% of all malignancies and continues being the first reason of death for cancer in European women. Triple negative (TN) BC present minor survival rates than other BC subtypes. Key reasons for that is the absence of predictive markers of response to current therapy and the absence of targeted therapies. This study aims to identify proteins with predictive value of central Nervous System (CNS) metastases and therapeutic target candidates.

Methods: This is a case-control retrospective study comparing patients (pts) with metastases to CNS prior to treatment and those after adjuvant treatment. Sample selection included 50 samples. Formalin-fixed, paraffin-embedded samples were retrieved from Hospital 12 de Octubre Biobank. Proteins were quantified by parallel reaction monitoring.

Results: The average age was 55 years (range 25-85). Forty-seven pts (88.67%) had du- tal histology and presented high grade tumors (40 pts, 75.47%). Eight women in the case group presented as first distant recurrence CNS (14.80%), local recurrence (3pts, 13.04%), lung (2pts, 8.7%), bone (2pts, 1.26%), and other locations (7pts, 30.8%). In the control group, first distant recurrence occurred locally (6pts, 46.1%), bone (2pts, 15.4%), lung (1pt, 7.7%) and other sites (4pts, 23.1%). Protein expression data was successfully obtained from 50 samples. IGf15 ubiquitin-like modifier (P09161) was over-expressed in triple negative breast cancer tumors that develop metastases to CNS (p = 0.036) compared to tumors that do not develop these CNS metastases.

Conclusions: TN tumors frequently metastasize to visceral organs, particularly lungs and brain, and are less likely to metastasize to bone. The interferon-stimulated gene 15 ubiquitin-like modifier (IGf15) encodes an IFN-inducible ubiquitin-like protein. The IGf15 protein is involved in numerous cellular functions, including interferon-induced immune responses and the regulation of cellular protein turnover. Therefore, IGf15 may represent a novel breast tumor marker helpful in selecting pts who will develop CNS metastases. It also should be explored as a therapeutic target in this clinical context.

Legal entity responsible for the study: Biomedica Molecular Medicine SL

Funding: None.

Disclosure: L. Trilla-Fuertes: Employee of Biomedica Molecular Medicine SL. A. Gámez, J.A. Fresno: Shareholders in Biomedica Molecular Medicine SL. All other authors have declared no conflicts of interest.

1697P Assessing functional Androgen Receptor (AR) pathway activity using a computational model

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Background: Cellular signal transduction research identified 10-15 signaling pathways responsible for driving tumor growth. Defining pathway activity in tumor tissue is necessary to optimize targeted therapy choice. Verhaegh et al (Cancer Research 2014) used a Bayesian network approach to model transcriptional programs of signaling pathways. These pathway models use mRNA expression levels of validated direct pathway target genes to infer a probability of pathway activity in individual patient samples. Here, initial results of the AR model are presented.

Methods: 28 bona fide AR target genes were selected and a Bayesian network model for the AR pathway was built and calibrated. The model uses target genes mRNA levels (Affymetrix HG-U133Plus2.0 array) as input to infer probability of AR pathway activity. Evaluation was done using multiple public datasets from clinical studies. The model was also adapted for qPCR data as input, using a subset of most informative target genes.

Results: Biological validation on androgen stimulated LNCaP cultures showed expected AR activity (GSE7808), which was inhibited by the anti-androgen bicalutamide (GSE7708). In cell line xenograft models (GSE18887, GSE33316, GSE9866), AR was active in the presence of androgen and inactive in castrated mice. In prostate hyperplasia and 90% of primary prostate cancer (PCa) samples (GSE1591, GSE24043, GSE32992, GSE33325, GSE45016) AR was active; in contrast, AR was inactive in 30-50% of castrated resistant or metastatic samples. AR was active in primary PCA samples, but not in samples taken 5 days after surgical castration (GSE32982). In other cancer types AR was mostly inactive, except for a subset of Her2 subtype Breast Cancer (BCa), Luminal BCa (EM-TAB-365, GSE12276, GSE7097, GSE82165), and meningioma samples (GSE16981, GSE94938). Translation to qPCR-RNA measurement as input was successful, underscoring the portability of our approach to other measurement platforms.

Conclusions: Our biologically validated computational AR model enables assessing functional AR pathway activity in individual patient tissue samples, based on mRNA microarray or qPCR input from respectively FF or FFPE material. Other pathway models and clinical validation studies are in progress.

Legal entity responsible for the study: Philips Research

Funding: None.


1698P Evaluation of deamination bias from formalin-fixed tissues of small cell lung cancer with a dual strand targeted amplicon sequence

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Background: Precision medicine is dependent on identifying actionable mutations in tumors. Accurate detection of mutations is often problematic in formalin-fixed paraffin-embedded (FFPE) tissues, as it causes DNA damage such as fragmentation and cytosine deamination. These Sequence artifacts can be difficult to distinguish from true mutations, and are an increasing interpretive issue. Understanding of the characteristics of these sequence artifacts in FFPE tissues is critical to improve the accurate detection of actionable mutations.

Methods: We reviewed the clinical courses of 136 small cell lung cancer (SCLC) patients who had undergone surgery at 17 institutions in Japan between January 2003 and...
and January 2013. In these patients, we obtained the FFPE tissues of 79 cases which were histopathologically confirmed as SCLC and fitted for sequencing analysis with suitable DNA quality. Targeted amplicon sequence was conducted with MiSeq and TruSight panel (Illumina) which is a dual stranded amplicon kit for detecting cytosine deamination. We evaluated the characteristics of deamination bias and the relations with institutions and age of the tissue block.

Results: We could evaluate sequence of 73 samples data from 14 institutions. Target region of the sequencing was 26 genes, total 14686 bp. The total discordant single nucleotide variant (SNV) between forward and reverse strand were 690 cases, 16.4 cases per sample. The highest number of discordant SNV was 132 per sample. The most part of discordant SNV was the deamination change (C>T/G>A), 589 (85.4%) of 690 cases. The highest discordant SNV frequency was 0.25 with read depth 1876 in deamination change pattern, and 0.10 with read depth 4196 in the others. The frequency of the deamination change was different by institutions more than age of the tissue block.

Conclusions: Cytosine deamination from formalin fixation can be a major issue in diagnostic test of genome DNA for cancer samples. Procedures that assess, minimize or remove formalin-induced influences is important in the interpretation of genomic DNA analysis leading to better practice.

Legal entity responsible for the study: Toraji Amano
Funding: None
Disclosure: All authors have declared no conflicts of interest.

1699P Functional genomic mRNA (FGmRNA) profiling of >18,000 tumor samples identifies potential new indications for antibody-drug conjugates (ADCs) in a broad range of tumor types

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Background: ADCs, consisting of an antibody designed against a specific antigen at the cell membrane linked with a cytotoxic agent, are an emerging class of therapeutics. Since ADC targets do not have to be drivers of tumor growth, ADCs are potentially relevant for a wide range of tumor types. Therefore, we aimed to define the landscape of ADC target expression in a broad range of tumor types.

Methods: Pubmed and ClinicalTrials.gov were searched for ADCs that are or were evaluated in clinical cancer trials. Gene expression profiles of 18,055 patient derived tumor samples representing 60 tumor (sub)types and ≥ 3,520 samples representing 22 healthy tissue types were collected from the public domain. Next, we applied FGmRNA-profiling (Fehrmann et al. Nat Genet 2015;47:115-25) to predict per tumor type the overexpression rate at the protein level of ADC targets with healthy tissue samples as reference.

Results: We identified 87 ADCs directed against 59 unique targets. 17 ADC targets showed predicted overexpression of ≥ 75% of samples in at least 1 tumor (sub)type, 38 ≥ 50% and 56 ≥ 25%. A predicted overexpression rate of ≥ 10% of samples for multiple ADC targets was observed for high incidence tumors like breast cancer (n = 31 with n = 23 in triple negative breast cancer), colorectal cancer (n = 18), lung adenocarcinoma (n = 18), squamous cell lung cancer (n = 16) and prostate cancer (n = 5). In rare tumor types we identified targets showing high predicted overexpression, for example in uveal melanomas we found 95% predicted overexpression for c-MET.

Conclusions: This study provides a data driven prioritisation of available ADCs for clinical evaluation in 60 tumor (sub)types. This comprehensive ADC target landscape can support clinicians and drug developers in trial design.

Legal entity responsible for the study: UMCG
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Disclosure: E.G.E. de Vries: Advisory board: Medivation, Merck and Synthon: payments to the institution. Research grants: Amgen, Genentech/Roche, Chugai, Servier, Novartis, Synthon, AstraZeneca, Radius Health, CytoimmunX, Nordic Nanovector: payments to the institution. All other authors have declared no conflicts of interest.
TUMOUR BIOLOGY AND PATHOLOGY

1700O Genomic profiling of 114,200 advanced cancers identifies recurrent kinase domain duplications (KDD) and oncogenic rearrangements (RE) across diverse tumor types


Methods: CGP was performed on DNA and/or RNA from 114,200 solid tumors or precursor samples. RNA sequencing for 265 genes was available for some cases. Selected genomic events were confirmed by manual inspection.

Results: KDD were observed in 598 cases (0.62%): 28 genes commonly rearranged in cancer. Total mutational burden (TMB) was determined on 1.1 Mb. Significant GA were observed in 2.7% of brain tumors, most often EGF (66), BRAF (52), PDKFR2 (15), and FGFR3 (26). In extracranial tumors, KDD were common for RET (13-16% of breast, lung, and thyroid KDD cases), MET (35-20% of uterine and brain KDD cases), and ALK (34% of lung KDD cases). KDD possibly related to TKI resistance were seen in BRAF V600E-positive melanoma and ALK-related NSCLC. Table 1 summarizes KFE and KDD for NSCLC, TCGF, KIPK, and CRGK in select tumors. For patients with clinical responses to matched TKIs, KDD and KFN were found widely in cancer, with gene partner varying by subtype.

Conclusions: KDD are enriched in brain tumors. Diverse KDD are found extracranially and may underlie acquired resistance. Index cases with clinical responses to matched TKIs suggest KDD, KFN and KRE can be targeted therapeutically in many histological subtypes. Recurrent KFN are found widely in cancer, with gene partner varying by subtype.

Table 1700O

<table>
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<th>Tumor Type</th>
<th>ALK FN</th>
<th>ALK RE</th>
<th>FGFR2 FN</th>
<th>FGFR2 RE</th>
<th>FGFR3 FN</th>
<th>FGFR3 RE</th>
<th>RET FN</th>
<th>RET RE</th>
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<td>5</td>
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1701O Comprehensive Genomic Profiling (CGP) of Thymic Gland Carcinomas


Methods: IFPE sections of 174 consecutive cases of mTC were sequenced using hybridization-captured, adaptor ligation-based libraries to a mean coverage depth of >500x for up to 315 cancer-related genes plus 37 introns from 28 genes frequently rearranged in cancer. Total mutational burden (TMB) was determined on 1.1 Mb. Clinically relevant genomic alterations (CRGA) were defined as GA linked to drugs on the market or under evaluation in mechanism driven clinical trials.

Results: All mTC were clinically advanced and included 4% adenocarcinoma (TAC), 3% basaloid (TBC), 3% lymphoepitheliomatous (TLEC), 17% neuroendocrine.

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>TAC</th>
<th>TBC</th>
<th>TLEC</th>
<th>TNEC</th>
<th>TNOS</th>
<th>TSCC</th>
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<td>5</td>
<td>30</td>
<td>54</td>
<td>69</td>
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<td>50</td>
<td>48</td>
<td>57</td>
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<td>60% F</td>
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<td>37% F</td>
<td>24% F</td>
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<td>PDGFR/FGFR3 KIT MET PTHC1</td>
<td>CDKN2A FBW7</td>
<td>CDKN2A MEN1</td>
<td>KIT BRCA2 IDH1 ERBB2 ERBB3</td>
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Clinical implications of genomic variants identified in over 30,000 advanced-stage cancer patients by next-generation sequencing of circulating tumor DNA


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Background: Next-generation sequencing (NGS) of circulating tumor DNA (ctDNA) enables non-invasive profiling of solid tumors. Over the past few years, research and clinical guidelines have highlighted a role for liquid biopsy in patient care; however, few large datasets on clinical use have been published.

Methods: Somatic genomic profiles of 35,492 plasma samples from 30,024 advanced cancer patients were determined by a ctDNA NGS test targeting up to 73 genes (Guardant360®). Accuracy of ctDNA-detected driver alterations (PPV) was assessed by comparing to available matched tissue tests for 646 patients (lung, colon, and other cancer types). A pooled response rate analysis was performed across published/in press datasets presenting response data to alterations detected by Guardant360®.

Results: The full cohort consisted of non-small cell lung cancer (NSCLC) (59%), breast (16%), colorectal (CRC) (10%) and multiple other solid cancer types (35%), with ctDNA alterations detected in 88%, 86%, 88%, and 82%, respectively (86% overall). 19% of patients had 5 or more ctDNA alterations associated with an FDA-approved therapy. Resistance variants were identified in 18% of NSCLC, breast, CRC, prostate, melanoma and GIST patients. PPV ranged from 92-100% for EGFR L858R/E19del/E20ins (98%), ALK/RET/RORS fusion (92%), BRAF V600E (99%), KRAS G12/G13/Q61 (94%), and MET E14 skipping mutations (100%). Pooled response rate to 1st line EGFR TKIs (n = 43 NSCLC): 86% [95% CI: 71-94%]; to osimertinib (n = 63 NSCLC): 54% [41-67%]; to crizotinib (n = 63 NSCLC): 24% [14-34%]; to Nilotinib (n = 21): 24% [9-44%]; and to imatinib (n = 1090): 46% [37-55%].

Conclusions: Use of liquid biopsy is increasing in clinical care, providing an option of obtaining genomic information non-invasively. This dataset, derived from liquid biopsy use in clinical practice, highlights the clinical impact of identifying alterations that are targetable by drugs with regulatory approval, including emergent resistance alterations.

Legal entity responsible for the study: Guardant Health, Inc.

Funding: None


1703PD Landscape of DNA damage response (DDR) genes alterations in the prospective MOSCATO and MATCH R trials

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Background: DDR deficiency is a hallmark of cancer. We aimed at describing in 2 prospective trials run at Gustave Roussy Cancer Campus the molecular and clinical characteristics of patients (pts) harboring DDR gene alterations with special focus on mismatch repair (MMR).

Methods: Pts with metastatic solid tumors enrolled in MOSCATO (NCT0366019) and MATCH R (NCT02571992) trials had on-potus tumor biopsy; molecular profiling was performed using Targeted Next Generation Sequencing (TGS) and Comparative Genomic Hybridization array (CGHa), or Whole Exome Sequencing (WES). Alterations in 46 genes involved in DNA repair were searched. After review by molecular geneticist, pathogenic variants (PV) were defined as variants causing protein truncation (frameshift indels, nonsense or splice site variants) or known to be deleterious/or damaging according to databases such as LOVD, BRCAshare and OncorB. Variants without deleterious prediction were excluded.

Results: Molecular data of 1092 pts of various histologies enrolled between Dec. 2011 and Oct. 2016 was used. Analysis of TGS (N = 1090), CGHa (N = 838) and WES (N = 304) data allowed identifying 156 alterations in 187 pts (9.8%) and 30 DDR genes: 60 PV, 86 variants of unknown pathogenicity (VUP) and 10 fals deletions (CGHa). Most frequent altered pathways were homologous recombination (47 PV, including 30 BRCA1/2 PV and 7 ATM PV in 13 primary sites) and MMR. The 27 pts with 35 MMR and POLE alterations (12 PV, 20 VUP and 5 deletions) had 11 different primary types including most frequently colorectal, genito-urinary and breast. Only one pt was previously known to have Lynch syndrome. Mismatch PV occurred most frequently in POLE, MLH1, MSH2, PMS2 (2 each), as well as MSH3 and MLH1 (1 each). 1427 pts received immunotherapy (IO). Median PFS was 6.5 months with IO and 6.2 months with conventional therapy. Correlation of MMR aberrations with immune infiltrates and outcome (response, PFS and OS) on IO will be presented at the congress time.

Conclusions: DDR gene alterations occur regularly in solid tumors. Systematic analysis of DDR alterations could allow customizing treatment of pts that specifically benefit from IO or DNA repair inhibitors through synthetic lethality.

Clinical trial identification: NCT01566019 and NCT02571992

Legal entity responsible for the study: Gustave Roussy Cancer Campus

Funding: Gustave Roussy Cancer Campus

Disclosure: All authors have declared no conflicts of interest.
Background: Patients with triple negative breast cancer (TNBC) comprise a heterogeneous and poor-prognosis subgroup. Biomarkers for targeted therapy development remain a challenge. Progression of TNBC is associated with extracellular matrix (ECM) remodeling and reactivation of the paracrine Hedgehog (Hh) pathway, highlighting the importance of tumor–microenvironment (TME) interactions. We investigated whether TME biomarkers could determine clinical response in TNBC patients treated with the Hh pathway inhibitor sondeghib in combination with docetaxel.

Methods: Patients enrolled in GECAM2012-12 (EUDCORE) trial were included (n = 12). To evaluate Hh pathway activation, the expression of SHH and GLI1 was centrally examined by immunohistochemistry in pre-treatment primary tumors. A Hh Pathway Activation Signature (HPAS) was defined when SHH expression in epithelium and GLLI in stroma were high (median). Biomarkers involved in formation and degradation of ECM (C1M, C1M, C4M, C6M, pro-C3, pro-C6, CRMP, Lox-2 and VCANM) were evaluated by ELISA (Protein Fingerprint) in sequential plasma samples. EECM signature (ECMS) was defined when C4M and VCANM were high at baseline (>median).

Results: Related to Hh pathway activation, only 10 tumors had IHC results. Three patients had high HPAS, 2 of them experienced a clinical benefit, 1 complete response (CR) and 1 stable disease (SD) lasting 7.5 and 5.5 months, respectively. All patients with low HPAS expression progressed. An additional patient had clinical benefit but the status of Hh pathway activation was unknown. For ECM biomarkers, a maintained reduction was observed in the expression of long-term treatment (C2D1-0.5h, C2D2-25h and C4D1) vs baseline for pro-C3 (12.8, 10.2 and 9.4 vs 16.6, p < 0.05, p = 0.3, p = 0.25, respectively), and pro-C6 (9.2, 7.5 and 8 vs 9.95, p = 0.13, p < 0.01, p = 0.05, respectively). Interestingly, patients with high ECM had better Progression Free Survival (p = 0.02). Moreover, 4 patients out of 12 had high ECMS, 3 of them experienced a clinical response, 1 CR and 2 SD. All patients with low ECMS progressed.

Conclusions: Hh pathway activation and ECM remodeling might be associated with improved benefit to sondeghib in combination with docetaxel in TNBC metastatic patients.

Clinical trial identification: NCT02073776.

Legal entity responsible for the study: GECIM Spanish Breast Group.

Funding: Australian National Health and Medical Research Council.

Disclosure: M. Hui: Institution conducts research funding by Pfizer. M.A. Karsdal: Employed by Nordic Bioscience in a compensated leadership role and owns interest in the company. A. Urruticoechea: Consulting advisory role in Essai. Travel accommodation expenses by Roche and Merck and Eisai. S. O’Toole: Honoraria from Bristol Myers. C.L. Bager: Employed by Nordic Bioscience. A. Swarbrick: Institution receives research funding from Novartis Pharmaceuticals. Honoraria from Roche. M. Martin Jimenez: Speaker honoraria and advisory boards of AstraZeneca. All other authors have declared no conflicts of interest.

Detection of therapeutic targets in carcinomas of unknown primary

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Background: Current cancer treatment paradigms are based on features of the primary tumour and extent of disease. Carcinoma of unknown primary (CUP) is a histologically confirmed metastatic cancer in the absence of an identifiable primary tumour. As such it is difficult to determine the optimal treatment strategy and 5-year survival rates are less than 20%. This poor survival rate is due to both the unclassifiable metastatic malignancy and the use of empirical broad-spectrum chemotherapy. A shift towards personalising cancer management based on mutation profiling has been explored in many cancer types including CUP. Small studies have reported durable treatment responses in CUP patients receiving targeted therapies, specifically when EGF and KIT variants are detected. The present study has explored whether biologically important oncogenic driver mutations and potentially actionable targets are present in CUP that have potential to better inform treatment decisions.

Methods: CUP cases (n = 32) diagnosed on histopathology criteria were selected for study. Sections were cut from paraffin blocks of formalin-fixed tissue and DNA isolated. Extracted DNA was amplified with the Ion AmpliSeq Cancer Hotspot panel and Oncomine Focus panel for the identification of biologically relevant and actionable mutations, respectively. Amplified DNA was sequenced using the Ion Torrent platform and data was processed using a stringent variant filtration pipeline.

Results: Biologically relevant or therapeutically druggable variants were detected in 88% (n = 28) of cases. The most common variants were in TP53 (47%), KRAS (19%), MYC (6%), BRAF (6%) and CDKN2A (6%). There were potentially actionable targets in 14/32 (44%) cases, with the most common druggable variants being in the KRAS gene (exon 11) (6 cases) and MYC gene amplifications (5 cases).

Conclusions: This retrospective study successfully identified biologically relevant variants in 88% of CUP cases. 50% of these variants were potentially actionable with drugs currently approved for use in known primary cancer types or undergoing clinical trials. This would give a novel treatment option to patients with a currently incurable disease with poor survival. The data therefore supports the use of NGS at diagnosis to give biological insight into the drivers leading to the malignancy, and to allow consideration of novel targeted treatment options.

Legal entity responsible for the study: GECIM Spanish Breast Group.

Funding: PathWest

Disclosure: All authors have declared no conflicts of interest.

Analysis of stroma and immune-related gene expression patterns during breast cancer (BC) progression

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Background: Characterization of the immune phenotype of tumors during progression could aid in developing patient-tailored therapy strategies. Here, we sought to identify differences in immune markers comparing paired tumors from primary and metastatic sites from the GECIM/2009-03 (ConvertHER) study.

Methods: Matched primary and metastases were analysed by immunohistochemistry as described by Herbst et al., 2014 for PDL1 expression. The nanostring gene expression platform was used to profile and identify differences in the expression of 805 immune-related genes. Significant features (p-value < 0.05) were assessed for functional enrichment of KEGG pathways and GO terms.

Results: Out of 44 pairs analyzed for PDL1, 29 (66%) were ER+/HER2-, 3 (7%) ER-/HER2+, 6 (14%) ER+/HER2+ and 6 (14%) ER-/HER2- (TN). PDL1 expression (% positive) was observed in the immune cell (IC) compartment in 11 (19%) ER+/HER2-, 4 (9%) ER-/HER2- 2 (3%) ER+/HER2+ and 11 (19%) TN samples. No significant differences were observed between primary and metastases. Out of 60 pairs analyzed by nanostring, the most (40, 67%) were ER+/HER2-, 5 (8%) ER-/HER2-, 7 (12%) ER+/HER2+ and 8 (13%) TN. In the global population, we found that 102 genes were differentially expressed (fold-change >2) between primaries and metastasis. For the ER+/HER2- subgroup, expression of 98 genes significantly differs in metastasis compared to primaries. No clear changes in pre-specified immune signatures were observed, probably due to the high tumor heterogeneity, different treatments and small sample size. Interestingly, analyses of pre-specified gene signatures suggest that metastases have decreased Notch pathway, innate inflammation and TGFß-activated fibroblasts signatures. Moreover, GO-enriched signature analyses suggest that B cell differentiation and type 1 IFN pathway are also reduced in metastases both in the global population and in ER+/HER2- tumors, thus suggesting a decreased immune defense during progression.

Conclusions: Our analysis failed to identify novel immune biomarkers of BC metastases. However, these data pointed out that tumors could relax the immune system response during progression.

Clinical trial identification: NCT01377363.

Legal entity responsible for the study: GECIM Spanish Breast Group.
Orthotopic versus subcutaneous NET: tumor tissue characteristics result in different answers when ADC is used to validate early therapy response following Peptide Receptor Radionuclide Therapy (PRRT).

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Background: Preclinical studies in oncology are often performed in subcutaneous tumor xenografts, yet these models cannot be validated by measuring changes in tumor size. We first characterized subcutaneous (sc) versus orthotopically grown neuroendocrine tumors of the pancreas (NET) with high versus low somatostatin receptor subtype 2 (SSTR2) by multimodal imaging and validated the apparent diffusion coefficient (ADC) as a potential biomarker for early therapy response following SST2-specific PRRT.

Methods: NET cells (native, SSTR2-transfected BON) were inoculated sc or orthotopically (n = 20) in C57Bl/6 mice. Tumor characteristics were monitored using a small animal nanoScanPET/ME (T1/T2w anatomy, diffusion-weighted imaging, dynamic contrast-enhanced MRL, angiography, PET: Ga-68-DOTATOC, F-18-FDG). PRRT: ADC values and tumor growth were measured to monitor PRRT effects following Lu-177-DOTATOC injection.

Results: Native BON tumors showed different morphologic and metabolic patterns between sc and orthotopic tumors. Sc BON/SSTR2 tumors were similar to native sc BON tumors, while orthotopic BON/SSTR2 tumors were strongly growth delayed and developed necrosis at an early stage compared to native orthotopic BON tumors. Accept of the orthotopic BON/SSTR2 tumors, small tumors appeared solid with high FDG uptake. During tumor growth necrosis increased and FDG decreased. Perfusion was increased in orthotopic versus sc tumors (ktrans = 0.49 min⁻¹ and 0.33 min⁻¹). Interestingly, Lu-177-DOTATOC uptake was ~4 times higher in sc than in orthotopic BON/SSTR2 tumors. While the ADC reflected the early effects of PRRT (first 9 days) precisely in orthotopic tumors, therapy response could not be validated by ADC in sc tumors due to initial high liquid content in the tissue.

Conclusions: Successful therapy validation presupposes precise knowledge about the used xenograft and the tumor morphology in order to allow correct interpretation of therapeutic effects. In the particular, the orthotopic SSTR2-2 tumors do reflect the physiological situation better than sc tumors and allow to use the ADC as a potential biomarker for early validation of PRRT effects.

Legal entity responsible for the study: DKFZ German Cancer Consortium/DKFZ German Cancer Research Center

Disclosure: All authors have declared no conflicts of interest.

1707P
Cathepsin S regulates cell migration and invasion through mediating store-operated calcium entry and the focal adhesion proteins

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Background: Cathepsin S (CTSS), a lysosomal cysteine protease, plays an important role in inflammation, and it has been reported that it is also associated with angiogenesis and extracellular matrix (ECM) degradation promoting cell migration and invasion. Since CTSS is stably overexpressed in the different types of cancer cells, we explored a novel intracellular mechanism other than ECM degradation that regulates cell migration and metastasis.

Methods: Human oral cancer cells, OEC-M1, and breast cancer cells, MDA-MB-231, were used for this study. The expressions of CTSS were knocked down by siRNA transfection and the enzymatic activities were inhibited by highly-selective CTSS inhibitor, 58. The migratory and invasive abilities were determined by wound healing assay and transwell invasion assay, respectively. Microarray data and promoter prediction analysis were used to determine the intra-cellular targets of CTSS. Immunofluorescence assay was executed to evaluate STIM1 puncta formation and calcium inferences from store-operated calcium entry (SOCe) were measured by fura-2 calcium imaging. Western blot analysis was performed to detect the alteration of focal adhesion proteins.

Results: Our data showed that either CTSS knockdown with siRNA or activity inhibition could significantly decrease cell spreading area, and suppress cell migration and invasive activities in both OEC-M1 and MDA-MB-231 cells. Moreover, inhibition of CTSS enzymatic activity resulted in the suppression of STIM1 aggregation and decreasing calcium influx from SOCe. Furthermore, downregulation of CTSS expression with siRNA could reduce the protein expression of three focal adhesion proteins, including CD29, CD104 and vinculin, which could be restored by CTSS transfection.

Conclusions: These results exhibit a novel intracellular molecular mechanism of CTSS mediating STIM1 aggregation and the calcium influx from SOCe to regulate cell adhesion proteins, which are crucial for ECM interactions, cell migration and invasion. Legal entity responsible for the study: Ministry of Science and Technology of Taiwan

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1711P
Type VI collagen (COL6) as part of tumorgenesis: Focus on quantifying specific COL6 protein fragments in serum

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Background: Type VI collagen (COL6) is emerging as an important component of the tumor microenvironment. The rationale that COL6 derived protein fragments may possess pro-tumorigenic properties has ample precedent (e.g. endothorfin). Little is however known, regarding COL6 degradation fragments as biomarkers for cancer. Here we address the biomarker potential of three specific COL6 degradation fragments measured in serum: Pro-C6 (C-terminal of the α3 chain/endothorfin), C6Mα3 (MMP-generated neo-epitope on the α3 chain), C6M (MMP-generated neo-epitope on the α1 chain).

Methods: Pro-C6, C6Mα3 and C6M were measured by validated competitive ELISA in serum from patients with various stage solid tumors prior to treatment and healthy controls (table).

Results: C6M and C6Mα3 were significantly elevated (Kruskal-Wallis test) in most cancer types compared to controls, whereas Pro-C6 was not (table). A trend (p = 0.098) towards higher Pro-C6 was seen in the late (3/4) vs early (1/2) stage (Mann-Whitney test), whereas no difference was seen with C6M (p = 0.822) and C6Mα3 (p = 0.438). AUROC was 0.89 (p < 0.0001) and 0.86 (p < 0.0001) and 0.59 (p = 0.216) for C6M, C6Mα3 and Pro-C6, respectively, when comparing all cancer types combined to healthy controls.

Conclusions: Specific type VI collagen fragments were increased in serum from cancer patients compared to healthy controls, and showed promising clinical accuracy. This clearly supports COL-6 remodeling degradation as an important component in understanding tumorigenesis. Future studies will determine biological and clinical applicability of quantifying various COL-6 fragments in serum in relation to cancer. Legal entity responsible for the study: Nordic Bioscience

Funding: None
The combination analysis of tumor infiltration lymphocyte with Neutrophil to lymphocyte ratio may predict prognosis of colorectal cancer in stage I-III

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Background: The tumor infiltration lymphocyte as local inflammation and neutrophil to lymphocyte ratio as systemic inflammation have been known as prognostic factors in colorectal cancer. But little is known about the correlation and impression of the local and systemic inflammation together on the prognosis of colorectal cancer. This study aimed to evaluate the effects of this combination on prognosis.

Methods: In a retrospective study, 206 patients from 2006-2015 with colorectal cancer after curative surgery have been investigated. The patients diagnosed with stage IV or simultaneously had secondary cancers were excluded. The pathological samples after surgery were studied for tumor infiltration lymphocytes (TIL) and other pathological features. Also neutrophil to lymphocyte ratio (NLR) was calculated from up to 3 days before surgery from peripheral blood. For analysis the combination of these markers, patients were divided to four groups for local inflammation or systemic inflammation predominantly (high TIL/High NLR, high TIL/Low NLR, Low TIL/High NLR and Low TIL/Low NLR) and then the overall survival (OS) and Disease free survival (DFS) for each group were calculated. Then compared with each other.

Results: For these identified patients the number of death events was 73 and 133 were alive. The survival time for patients was 72.56 month and 72.26 month and HR (0.45) also low TIL was significant associated with poor prognosis on OS and DFS (p-value<0.005) for both.

Conclusions: The analysis of combination of local and systemic inflammation may predict the prognosis of colorectal cancer in patients who underwent the curative surgery. So in future this unexpensive and available methods seem can be used for determining the prognosis for these patients and used as markers.

Legal entity responsible for the study: Seyed Mohammad Reza Mortazavizadeh

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Prognostic value of NK and T-lymphocyte markers in operable non-small cell lung cancer (NSCLC)

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Background: New therapies aimed at activation of T and NK cells are expanding NSCLC treatments options. It is conceivable that markers designating ‘immune ignorant’, ‘immune excluding’ or ‘inflamed’ tumor phenotypes may influence the effectiveness of specific immune therapies.

Methods: qRT-PCR was used to assess the levels of 48 mRNAs in frozen tumor tissue sections from 115 stage I-IIIA NSCLC patients (35% never-smokers, 75% lung adenocarcinoma) who underwent pulmonary resection, and in matched normal lung parenchyma. mRNA expression (normalized vs. 4 reference genes) was compared between groups that did (45%) and did not relapse.

Results: Low expression of TIGIT (p adj=0.031) and CTLA4 (p adj=0.048) was correlated with shorter distant metastasis free survival after correction for multiple comparisons (p adj<0.042). Expression of PD-L1 (p =0.016), PDL-2 (p =0.029) and CTLA4 (p =0.002) was significantly lower in relapsed vs. non-relapsed NSCLCs, whereas there was no difference for PDL-1. Expression of NK markers: NCR3 (p =0.006) and CD96 (p =0.005), but not NCR3-ligand 1 or NKGD2, NKGD2c and NKGD2a were significantly lower in relapsed vs. non relapsed NSCLCs. Expression of CXCXR3 and its ligands: CXCL9 and CXCL10 (chemoattractants for lymphocytes), but not endotelin receptor type B, was significantly lower in relapsed NSCLCs (p <0.05), which could provide a plausible explanatory mechanism for lower expression of lymphocyte markers in tumours with propensity for metastases. GITR, FOXP3 and CXCL9 expression was significantly higher in tumour samples vs. normal lung parenchyma (p adj<0.02). NCR3, CX3CR1 and FASLG expression was significantly lower in tumor samples from smokers vs. never-smokers (p adj<0.02). Samples of normal lung parenchyma from smokers were marked by higher expression of chemoattractants for lymphocytes. Expression of immune tolerance markers is increased in NSCLC compared to normal lung tissues.

Disclosure: All authors have declared no conflicts of interest.

KRAS in non-small cell lung cancer

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Background: Disease heterogeneity with variable molecular mutations is one of the main contributory factors in non-small cell lung cancer (NSCLC). The goal of this study was to better understand the KRAS patients with co-occurring mutations.

Methods: We identified 60 patients with a diagnosis of NSCLC and a KRAS mutation in the COH Cancer Registry from 2009 to 2016. Next generation sequencing was performed.

Results: Of the 60 patients identified, 42 (70%) were Stage IV at diagnosis, 7 (12%) Stage I and 7 (12%) stage II and 4 (6%) Stage III. 47% (78) patients were smokers. Caucasian was the most common 44 (73%) racial group, followed by Asians 9 (15%), African-Americans 3 (5%), other 3(5%) and Pacific Islander 1 (1.7%). The average age at diagnosis was 67 (median 69.5) years; 30 patients (50%) were >70 years, 23 (38%) patients were 51-69 years, and 7 (12%) 50 years or less. The most common histology was adenocarcinoma 52 (87%), then adenocarcinoma 5 (9%), large cell 3 (5%) and small cell, squamous cell and carcinoid carcinoma (1 each, less than 2% each) Majority had metastatic disease 52 (87%) with 29% (12) metastasis to brain, with average 1.6 metastatic sites. An average of 1.97 (range =0-5) lines of therapy including chemotherapy, biologic agents or immunotherapy were received. 12 (20%) patients received immunotherapy, radiation in 28 (47%) and surgery in 22 (37%) with a median overall survival at 15 months. The most frequent molecular alteration was codon 12 mutation (47, 78%), followed by codon 13 (7, 12%) and codon 61 (6, 10%) mutations. The most

Table: 1711P

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<td>43.4 (**)</td>
<td>56.0 (**)</td>
<td>16.5 (ns)</td>
<td>31.2 (ns)</td>
<td>87.6 (***+)</td>
<td>47.6 (**)</td>
<td>60.5 (*)</td>
<td>33.9 (ns)</td>
<td>49.5 (**)</td>
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<td>3.1 (***)</td>
<td>1.1 (ns)</td>
<td>2.3 (ns)</td>
<td>3.1 (***)</td>
<td>2.4 (ns)</td>
<td>2.9 (*)</td>
<td>2.3 (ns)</td>
<td>2.6 (*)</td>
<td>0.99 -</td>
</tr>
<tr>
<td>Pro-C6 (p-value)</td>
<td>7.2 (ns)</td>
<td>9.8 (ns)</td>
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<td>9.2 (ns)</td>
<td>9.5 -</td>
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1mean, ng/ml
2vs. healthy controls;
p-value <0.005, **<0.01, ***<0.0001, ns: not significant
common co-occurring mutations in this cohort were TP53 (15.25%), ATM (9.15%), LRP1B (9.15%), ARID1A (8.19%), STK11 (8.13%), ARID1B (7.12%), BRT (7.12%), EGRF (6.10%), RBM10 (6.10%), SPTA1 (6.10%). We are currently evaluating the relevance of the Circos plots for these mutation data, clinical response to immunotherapy and potential biomarkers.

Conclusions: KRAS mutations are among the most common molecular alterations identified in NSCLC. The discovery of effective treatments targeting KRAS mutations has represented a challenge so far. Understanding the significance of co-mutations and their therapeutic implications, especially in response to immunotherapy agents represents an important step to develop better treatment options for KRAS mutated lung cancers.

Legal entity responsible for the study: City of Hope National Medical Center

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Disclosure: All authors have declared no conflicts of interest.

1715P PIK3CA mutation and PD-L1 expression in lung squamous cell carcinoma surgically resected

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Background: Squamous-cell carcinoma (SCC) of the lung is the second most frequent histology in non-small cell lung cancer (NSCLC). Over the last decade new approaches targeting specific pathways in NSCLC have emerged but very few advances were made in its treatment. The PI3K-akt-mTOR pathway is implicated in multiple cancer processes and PIK3CA mutations are being investigated in SCC as a potential therapeutic target. The aim of the study was to evaluate the histological characteristics, mutations in PIK3CA and PD-L1 expression in these tumors.

Methods: Surgically resected lung SCC samples (FFPE) from 100 patients, stage I-III, were included in this study. Clinicopathologic characteristics included tumor size, TNM, smoking status, lymphovascular and pleural invasion, histopathological grade, stromal lymphoplasmacytic reaction and type of tumoral growing. DNA was isolated from 92 samples according to standard procedures and PIK3CA mutation analysis was done using Cobas 4800 platform. PD-L1 expression was analyzed in 74 cases by immunohistochemistry with FDL1 22C3 pharmDX assay. The PD-L1 expression was evaluated by tumor proportion scores (TPS) as IASLC guidelines.

Results: The mean age was 68 years (53-86), 14 females and 86 males. Among staging: 53 patients had stage I, 27 stage II, and 19 stage III. 53% and 35% showed vascular and pleural invasion respectively. Low to moderate stromal lymphoplasmacytic reaction was found in 34% and severe in 11%. PIK3CA mutation was found in 9/92 (9,8%) patients: E545X (n = 2), E542K (n = 5), H1047X (n = 1), C420R (n = 1). PD-L1 expression was found in 31 of out 74 cases (42%). 14 cases with TPS between 1-49%, 17 cases with TPS >50%. 57% (55%) of PIK3CA mutated cases were PD-L1 positive (2 of them >50%). In PIK3CA non-mutated cases 26 out of 67 (39%) showed PD-L1 expression: 11 cases with TPS between 1-49%, 15 cases with TPS >50%.

Conclusions: PIK3CA mutation was found in 9.8% of SCC of the lung, most of them in exon 9. PD-L1 expression was found in 42% of the SCC in our series. 55% of PIK3CA mutated patients were positive for PD-L1 expression. No correlation has been found between PD-L1 expression and PIK3CA mutation in SCC. It is important to know more about the relation of these factors to select the patients for immunotherapy and new target agents.

Legal entity responsible for the study: IIS

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1716P TRKA expression and NTRK1 gene copy number across solid tumors

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Background: Neurotrophic Tropomyosin Kinase Receptor 1 (NTRK1) gene encodes for the protein Tropomyosin-related kinase A (TRKA). A deregulated activity of TRKA has been detected in cancer, leading to oncogenic activity. This can result from focal amplifications, deletions and point mutations involving the NTRK1 gene. The incidence of NTRK1 gene copy number gain (CGN) across solid tumors has not been investigated. We present here the results of an immunohistochemistry (IHC) screening for TRKA expression within the phase I ALKA-001 clinical trial. Clinical results of ALKA-001 clinical trial are not presented here.

Methods: Formalin-fixed paraffin-embedded (FFPE) consecutive samples of different solid tumors were tested for TRKA IHC staining. Samples showing TRKA IHC staining in at least 10% of cells were further studied by fluorescence in situ hybridization (FISH) to assess whether NTRK1 gene rearrangements were present and to assess CGN. All patients signed informed consent for molecular screening according to the phase I ALKA-001 clinical trial.

Results: 1043 samples were tested; annotation for histology was available in 1023. Most of the samples were colorectal adenocarcinoma (CRC) (n = 550, 53.8%) or lung adenocarcinoma (312, 30.5%); 24 samples (2.3%) were biliary tract carcinoma (BTC). Seventeen (1.6%) samples were characterized by TRKA IHC expression (4 weak, 8 moderate, 5 strong). By FISH, 117 (5.9%) displayed NTRK1 gene rearrangement and 15 (0.8%) NTRK1 CGN gain. Among samples harboring NTRK1 CGN gain, 8 (53%) were lung adenocarcinoma, 3 (20.0%) BTC and 2 (13.3%) CRC. Five (33.3%) samples had concomitant ALK and ROS1 CGN gain. None of the lung adenocarcinoma (n = 8) had concomitant EGFR mutations. Both CRC samples (n = 2) harbored KRAS mutation. No correlation was found between grading of TRKA IHC staining and the number of NTRK1 CGN.

Conclusions: NTRK1 CGN gain can be found in 1.6% of solid tumors. In particular, weak and CRC gains in 2.6% of lung adenocarcinomas. A cutoff of 0.4% of CRC and 17.6% of BTC even though a limited number of the latter histology was included in the analysis. The prognostic and translational therapeutic impact of this genetic alteration remains to be established.

Legal entity responsible for the study: Salvatore Siena

Funding: The molecular screening was funded by Ignyta within ALKA-372-001 study. Investigators are supported by Fondazione Oncologia Niguarda Onlus - Project: “Terapia molecolare dei tumori” (G.M., S.S, A.-S.-B.). This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 635342

Disclosure: S. Siena: Consultant/advisory board member for Amgen, Bayer, Eli Lilly, Merck, Merrimack, and Roche. All other authors have declared no conflicts of interest.

1717P The correlation between MMR gene expression MSH2/MSH6 and VEGF A/VEGF B in gastro-esophageal cancer

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Background: VEGF proteins are key regulators of angiogenesis and targeting VEGF A led to inhibition of new blood vessels formation, with important therapeutic effects in various cancers. The roles of VEGF B are controversial, this peptide expression seems to inhibit apoptosis by suppressing many apoptotic/cell death related genes and to facilitate metastasis by inducing vascular leakiness, leading to a high degree of tissue hypoxia that consequently activates DNA damage signalling pathways. MSH2/MSH6 is an important complex of proteins in DNA mismatch repair system and their altered expression could represent a response to the rapidly growing number of replication errors in a tissue with a high index of proliferation.

Considering that in certain conditions, DNA damage response products, such as H2AX, promote tumor growth and angiogenesis, in the present study we aimed to identify a common pattern of expression behavior between MMR genes and VEGF components (VEGF A and VEGF B), in order to use these genes as diagnostic markers in gastro-esophageal cancer.

Methods: mRNA levels of MSH2, MSH6, VEGF A, VEGF B were evaluated in tumoral and peritumoral issues samples biopsied from 36 patients using qRT-PCR with specific Taqman gene expression assays.

Results: VEGF A/VEGF B and MSH2/MSH6 mRNAs were expressed in both tumour and peritumour mucosa, with a tendency of tumoral up-regulation for VEGF A and MSH2/MSH6. When comparing the differences between tumoral/peritumoral expression level among the studied genes, we found that MSH2 and VEGF A have a similar pattern of expression as follows: VEGF A gene expression correlates with MSH2 (rho Spearman = 0.4562; p < 0.05) and also, is similar to MSH6 (rho Spearman = 0.5082 p < 0.05); furthermore, VEGF B gene expression is correlated with MSH2 expression (rho Spearman = 0.5350 p < 0.05), with a very strong correlation between MSH6/VEGF B expression (rho Spearman = 0.6730 p < 0.0001).

Conclusions: Our results indicate a possible crosstalk between DNA mismatch repair and VEGF signaling pathways, providing new insight into understanding the potential connection of VEGF B and MSH6 in carcinogenesis.

Legal entity responsible for the study: University of Medicine and Pharmacy of Craiova, Romania

Funding: None

Disclosure: All authors have declared no conflicts of interest.
Liver-type glutaminase (GAB) suppresses malignant phenotype of glioblastoma cells

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Background: Glutamine (Gln) plays a pivotal role in the metabolism of tumors of different including glioblastoma (GBM), the most aggressive brain tumor. Glutamine (GA, EC 3.5.1.2) converts Gln to glutamate (Glu) and ammonia. GA is encoded by two genes GLS and GLS2, encoding kidney-type isoforms (KGs and GAC) and liver-type isoforms (GAB and LGa), respectively. Kidney-type isoforms promote cell proliferation, while the liver-type isoforms relate to quiescent state of cells. In GBM GLS is highly expressed, while GLS2 is hardly detectable. Transfection of human GBM T98G cell line with a sequence encoding GAB is known to decrease their survival, proliferation index and migration and sensitizes them to damage by hydrogen peroxide. To examine whether the mode of action of GAB extends to other GBM cell lines, the effect of GAB transfection of U87MG, U251MG and LN229 cells with GAB was assessed.

Methods: Mitochondrial activity was determined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) conversion (details in M. Szeliga et al., Glia, 2009). Cell proliferation was measured by a commercially available ELISA kit based on the detection of BrDU (5-bromo-2-deoxyuridine) incorporated into the genomic DNA. Migration was analyzed using the scratch assay. The tip scratch of cell monolayer was photographed under Juki Smart cell analyzer and measured after 0 and 24 h. Ability to form colonies was assessed after 14 days of culture following Giemsa staining of fixed cells.

Results: Transfection with GAB i) decreased mitochondrial activity, proliferation and colony formation ability of U87MG cells ii) inhibited ability of U251MG cells to form colonies iii) decreased mitochondrial activity, proliferation, migration and colony formation ability of LN229 cells. All transfected cells were more sensitive to hydrogen peroxide as compared to the controls.

Conclusions: Suppression of malignant phenotype and their sensitization to hydrogen peroxide damage by GAB transfection appears to be a feature common to all the glioblastoma cell lines so far studied.

Legal entity responsible for the study: Jan Albrecht
Funding: Ministry of Science and Higher Education of Poland, The Leading National Research Centre (KNOW-MBRC)
Disclosure: All authors have declared no conflicts of interest.

Downregulation of BRCA1 protein in clear cell renal cell carcinoma

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Background: Around 75% of renal cell carcinoma in adult kidney is clear cell renal cell carcinoma (ccRCC). This type of cancer is characterized by lipid overaccumulation and mutations in VHL (around 90% cases), BAP1 and PBRM1 genes as well as stabilization of HIF1α transcription factor. Additionally, metabolic switch to aerobic glycolysis and aberration in TCA cycle was observed in ccRCC independently on the stage of the disease. Moreover, the mTOR pathway hyperactivation and downregulation of AMPK pathway featured the ccRCC. This type of cancer is highly resistant to classical chemotherapy. BRCA1 is tumor suppressor gene, mutation in this gene is associated with breast and ovarian cancer. BRCA1 is a protein involved in DNA repair and apoptosis also interacts with BRG1 – core subunit of SWI/SNF chromatin remodeling complex. BRCA1 is transcribed from bidirectional promoter together with NBR2 – IsoRNA. Interestingly, NBR2 interacts with AMPK and is downregulated in ccRCC. CTGF is a protein which binds Topologically Associated Domains, and CTGF binding site was found in BRCA1/NBR2 promoter region.

Methods: Immunohistochemistry (IHC) on paraffin embedded clinical samples for BRCA1 and BRG1 core subunit of SWI/SNF complex, comparative transcriptomic study, co-immunoprecipitation (Co-IP) and chromatin immunoprecipitation (ChIP) method were used in this work.

Results: In this study we found downregulation of BRCA1 and BRG1 proteins in ccRCC patient samples independently on stage of the disease. Interestingly, downregulation of BRG1 was more severe in samples with strong lymphocyte infiltration. In contrast, downregulation at the transcript level was observed for BRG1 encoding gene but not for BRCA1. BRG1 and CTGF co-precipitated from cancer cells, indicating the existence of co-interaction between CTGF, BRG1 and BRCA1 proteins. Additionally, over-expression of BRG1 caused increased expression of CTGF in human cells. We also found that BRG1 targets both CTFC and BRCA1 genes.

Conclusions: BRCA1, BRG1 and CTFC module is dysregulated in ccRCC cells independently on Fuhrman grade and stage of the disease. This misregulation can have a broad spectrum of changes including 3D chromatin structure, transcription, epigenetic and others.

Legal entity responsible for the study: Elbieta Samowska
Funding: This work was supported by grant from National Science Center No UMO-2013/11/B/NZ2/00132
Disclosure: All authors have declared no conflicts of interest.

Alteration of p53 mRNA expression in neuroblastoma and its impact in disease outcome

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Background: Neuroblastoma is frequent childhood malignant tumor with high clinical heterogeneity. Despite the rare mutations of TP53 gene, p53-mediated pathway is often inactivated in neuroblastoma. The significance of MDM2, p53 direct antagonist, overexpression in neuroblastoma clinical course and outcome has been already established. But still remain patients with favorable clinical features and poor disease outcome.

Methods: The case group comprised 68 children with neuroblastoma (mean age: 36.7±4.7 months, primary tumors: 88%, MYCN+ 38%; MDM2 overexpressed: 79%; p53 mRNA expression level (EL) was analyzed in tumor samples with qRT-PCR and evaluated by the ΔACq method according to control GAPDH mRNA EL.

Results: We established that the value of p53 EL in neuroblastoma cells varied in wide limits. Significantly lower p53 EL was detected in recurrent and metastatic tumor samples comparing to primary tumors (P=0.001). Insignificant increase of p53 EL in patients with unfavorable clinical and biological features (late occurrence age, IV stage, MYCN amplification) was observed. However, we revealed significant increase of p53 EL in MDM2 overexpressed tumors (P=0.007). With ROC-analysis we assessed optimal criteria for distribution of patients according to p53 expression (OCC:1.18 a.u., P=0.04, AUC:0.69 for high and OCC:0.99, P=0.06, AUC:0.84 for low MDM2 expression). We have analyzed 3-year event-free survival (EFS) of patients with neuroblastoma and established 100% EFS survival for patients with low MDM2 and high p53 EL, while in other groups significant decrease in survival was observed (P=0.006). EFS rates of patients with low p53/high MDM2 and high p53/low MDM2 expressions were similar (27.7% and 33.3%) and for p53/MDM2 overexpressed tumors it was only 18.2% (P<0.05).

Conclusions: Regulation of p53-mediated pathway is complex and multicomponent system. Alteration of p53 EL is independent from clinical features marker of neuroblastoma. Analysis of p53/MDM2 co-expression provides the possibility for better neuroblastoma outcome prediction.

Legal entity responsible for the study: National Cancer Institute of Ministry of Public Health of Ukraine
Funding: None
Disclosure: All authors have declared no conflicts of interest.

The role of PD-L1 in a high-grade invasive human oral squamous cell carcinoma microenvironment

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Background: Blockade of the programmed-death 1 receptor (PD-1)-programmed death-ligand 1 pathway efficiently reduces tumour growth and improves survival. Durable tumour regression with blockade of the PD-1/PD-L1 checkpoint has been demonstrated in recent clinical studies. Oral squamous cell carcinoma (OSCC) is highly immunosuppressive, and PD-L1 expression has been proposed as a potential mechanism responsible for this phenotype. Despite the fact that anti-PD-1 treatment can produce durable responses, such therapy appears to benefit only a subset of patients. Thus, it is important to understand the mechanisms underlying the regulation of PD-L1 expression in the OSCC microenvironment.

Methods: The subjects were patients with primary OSCC who underwent surgical resection at the Kanazawa University Hospital between 1998 and 2008. And, three human oral squamous cell carcinoma cell lines established from tumor biopsies with different grade of invasive abilities were used: OSCC-20, OSCC-19 and TSU.

Results: We showed that PD-L1 expression in high-grade invasive OSCC cell lines was lower than that in a low-grade invasive OSCC line and found a close correlation between PD-L1 expression and the epithelial-mesenchymal transition (EMT). PD-L1 expression was upregulated in macrophages and dendritic cells (DCs) in high-grade invasive human OSCC-invasive or co-cultured with mesenchymal-phenotype OSCC cells in vitro. TLR4-inhibitory peptide successfully suppressed PD-L1 upregulation on macrophages and DCs co-cultured with mesenchymal-phenotype OSCC cells, suggesting that some EMT-induced tumour antigens is critical for PD-L1 induction on tumour-associated macrophages and DCs.

Conclusions: Further studies are necessary to explore the impact of EMT on the tumour immune microenvironment and to identify potential biomarkers for selecting...
patients who might preferentially benefit from PD-1/PD-L1 blockade or immunotherapies more broadly.

Legal entity responsible for the study: Kanazawa University

Funding: None

Disclosure: All authors have declared no conflicts of interest.

Results: We found that HNF1B transcript and HNF1B protein were downregulated in the majority of ChRCC in TCGA, and the magnitude of HNF1Bloss is unique to ChRCC. Additionally, we observed a strong correlation between reduction of HNF1B expression and aneuploidy in ChRCC patients. In MCF cells deficient in HNF1B, we observed the development of aneuploidy. HNF1B deficiency also reduced spindle checkpoint protein (MAD2L1, BUB1B) and cell cycle checkpoint protein (RB1 and p27) expression, and altered chromatin access of MAD2L1, BUB1B and RB1 genes. Coordinate loss of Bub1b and RB1 recapitulated the polyplody and larger cell size seen with Hnf1b deletion. TCGA data also showed that TP53 is mutated in 33% of ChRCC whose HNF1B expression was repressed, and the combination of HNF1B loss with TP53 mutation was associated with poor prognosis. The combination of HNF1B loss with TP53 inactivation led to increased cell proliferation and increased aneuploidy, providing evidence that coordinate loss of HNF1B and TP53 may enhance cellular survival and engender an aggressive ChRCC tumor phenotype.

Conclusions: HNF1B deficiency is a major driver of chromosomal instability in ChRCC and lethality is associated with subsequent TP53 loss. Further development of model systems with combined HNF1B/TP53 loss will accelerate the development of treatments specific for ChRCC.

Legal entity responsible for the study: UT MD Anderson Cancer Center

Funding: National Institutes of Health

Disclosure: All authors have declared no conflicts of interest.

1723P Some mechanisms of increasing malignancy of B16/F10 melanoma in female mice with chronic pain

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Background: The impact of chronic pain (CP) on the growth and development of tumors is poorly studied. However, one of the main goals of cancer therapy is the relief of chronic pain, a complex symptom based on combined pathophysiological mechanisms. Our aim was to study the influence of CP on melanoma growth in female mice and to determine levels of the VEGF family members in the tumor (T), its perifocal zone (PZ), and in the skin.

Methods: The study included 64 female C57BL/6 mice. B16/F10 melanoma was transplanted under the skin on the back of animals in the main group 2 weeks after sciatic nerve ligation. Mice with melanoma without CP were used as the controls. Levels of VEGF-A, VE-Cadherin, and VEGF-C were determined by Western blotting. The life span of mice with melanoma and CP was 1.5 times shorter than the control group. Melanoma in mice with CP was more aggressive, and metastases occurred after 1 week vs. 4 weeks in the controls. The rate of metastasis was higher (100% vs. 60% in the controls) melanoma with CP spread to multiple organs and caused unusual metastases to the heart and uterus. The rapid and specific development of B16/F10 melanoma in mice with CP was accompanied by increased levels of VEGF-A, -C and -R1 in T, PZ, and the skin, with their maximal accumulation in T in week 1. The VEGF-A level continued to increase in T and PZ (P<0.05) in week 2. VEGF-C and VEGF-R1 levels increased in PZ only and decreased in T and skin (T>PZ). The VEGF-A levels were equally high in both T and PZ, while VEGF-C and VEGF-R1 content in T was higher than in the skin and higher in PZ than in T. The VEGF-R3 level increased in T of mice without CP and was higher in T than in PZ, while in mice with CP its content in T was lower than in PZ. Levels of VEGF-R1 (in all tissues) and VEGF-R3 (in the skin and PZ) decreased in mice with CP in week 3.

Conclusions: CP shortened the life span of female mice with melanoma and enhanced the aggressiveness of B16/F10 melanoma metastases. The activation of angiogenesis in T and PZ can be considered as one of the mechanisms of the neoplastic progression.

Legal entity responsible for the study: Rostov Research Institute of Oncology

Funding: None

Disclosure: All authors have declared no conflicts of interest.

1724P The role of hepatocyte nuclear factor 4A (HNF4A) as a tumor suppressor in colorectal cancer

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Background: The hepatocyte nuclear factor 4A (HNF4A) is a transcription factor implicated in various physiological and pathological processes. The pathogenesis of colorectal cancer (CRC) is complex and influenced by many factors related to genetic, epigenetics and chronic inflammatory processes. TP53, p21 or Ras mutations and epigenetic alterations of genes coding for these oncogenes are involved in the aetiology of urothelium originating bladder cancer. Additionally, the TCGA study indicated that such important regulatory pathways/machines like these controlling cell cycle (PI(3)K)/AKT/mTOR signaling involved in the metabolic control, and chromatin modifications including SWI/SNF chromatin-remodeling complex (CRC) are affected in this disease.

Methods: Immunohistochemistry (IHC) on paraffin embedded clinical samples for SWI/SNF core subunits and key enzymes involved in metabolism control, comparative transcriptomic study and confirmatory quantitative real-time PCR (qRT-PCR) were used in this work.

Results: In this study we found a substantial decrease of protein levels of SWI/SNF core subunits in colorectal cancer clinical samples. Subsequently, we performed real-time qRT-PCR and IHC transcriptional data for clinical samples obtained from GEO database and confirmatory assessment of the transcript level in clinical samples. This analysis showed that the reduced protein level of SWI/SNF core subunits observed in advanced bladder cancer is likely caused by the decreased abundance of corresponding transcripts. We also found that the SWI/SNF complex interacts in human cells with key proteins involved in the control of energy status and glucose metabolism. The IHC analysis indicated altered abundance of these enzymes in cancer cells when compared to normal urothelium consistently to strong metabolic alterations characteristic for this type of cancer.

Conclusions: The down-regulation of SWI/SNF complex on both transcript and protein level, and decreased activity of its partner proteins link the molecular features with metabolic alterations observed in this type of cancer.

Legal entity responsible for the study: Michal Szymanski

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Disclosure: All authors have declared no conflicts of interest.

1725P Impact of global epigenetic machinery on clinical outcome of colorectal cancer patients treated with fluoropyrimidine-based therapy

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Background: The pathogenesis of colorectal cancer (CRC) is complex and influenced by many factors related to genetic, epigenetic and chronic inflammatory processes. Methods: This is a prospective study, conducted on 102 Egyptian patients, diagnosed with CRC. Blood samples were collected at baseline and after 3 & 6 months of receiving fluoropyrimidine (FP) based therapy. DNA methylation was measured by LC/MS/MS
There was not significant difference in prognostically “unfavorable” subtypes (HR-/HER2-) among all age groups, and HR-/HER2- was the least; however, the relative contribution of each subtype varied within age categories. In YA’s HR+/HER2+ was the most commonly diagnosed subtype (62%), followed by HR+/HER2- (15%), triple-negative (12%) and HR-/HER2+ (11%). Statistically no significant difference of BC subtypes was observed in YA, RR +/HER2+ - subtype was lesser in YA’s than in elderly population (62% vs 75%), but statistically non-significant (p = 0.19) and there was not significant difference in prognostically “unfavorable” subtypes (HR-/HER2- and triple-negative) (23% vs 17%) (p = 0.134, CI 95%: 0.90 to 1.71). Surprisingly no difference of Triple-negative BC was observed in YA and elderly groups (12% vs 13%).

Conclusions: The distribution of breast cancer subtypes among young adults didn’t vary from that observed in older women. Our study results seem to be in contradiction with other studies previously reported in literature. Future studies should consider whether distribution of breast cancer subtypes influences long-term survival in young compared with older women.

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**1726P** Comparison of breast cancer subtypes between young and elderly women

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**Background:** Breast cancer (BC) is increasingly recognized as a heterogeneous disease based on expression of receptors for estrogen (ER), progesterone (PR), and human epidermal growth factor receptor 2 (HER2). There are four main subtypes of BC with differing tumor characteristics and different risk factors, treatment options and prognoses. Few data exist on the frequency of molecular subtypes in young and older women. The purpose of this study is to compare the distribution of the BC subtypes in young and elderly patients.

**Methods:** During the period 2013 to 2015 including ER/PR and HER2 status, was obtained from the Georgian main histopathology laboratories all over the country. We analyzed 1003 women with BC included 85 women aged 20 to 39 years (YA’s), 118 women aged 40 to 45 years (older premenopausal), 665 women aged 46–70 (postmenopausal) and 135 women older than 70 years (elderly group) at diagnosis. Incidence ratios were calculated by subtype (triple-negative, HR+/HER2-; HR+/HER2+; HR-/HER2-; HR-/HER2+, and differences in subtype characteristics by age groups were evaluated.

**Results:** The incidence of BC in YA’s was 8.5%. The most common BC subtype was HR+/HER2- among all age groups, and HR-/HER2- was the least; however, the relative contribution of each subtype varied within age categories. In YA’s HR+/HER2- was the most commonly diagnosed subtype (62%), followed by HR+/HER2- (15%), triple-negative (12%) and HR-/HER2+ (11%). Statistically no significant difference of BC subtypes was observed in YA, RR +/HER2+ - subtype was lesser in YA’s than in elderly population (62% vs 75%), but statistically non-significant (p = 0.19) and there was not significant difference in prognostically “unfavorable” subtypes (HR-/HER2- and triple-negative) (23% vs 17%) (p = 0.134, CI 95%: 0.90 to 1.71). Surprisingly no difference of Triple-negative BC was observed in YA and elderly groups (12% vs 13%).

**Conclusions:** The distribution of breast cancer subtypes among young adults didn’t vary from that observed in older women. Our study results seem to be in contradiction with other studies previously reported in literature. Future studies should consider whether distribution of breast cancer subtypes influences long-term survival in young compared with older women.
and August 2016. Patients were classified into three groups. Group I: 48 patients with HCC in addition to liver cirrhosis, including 26 males and 22 females with a mean age of 58.60±5.29; Group II: 50 patients with liver cirrhosis, including 26 males and 24 females with a mean age of 56.74±5.21; Group III: 30 healthy subjects as controls, including 15 males and 15 females with a mean age of 56.30±7.30. Diagnosis of HCC was performed using two imaging methods (abdominal US & triphasic CT). All subjects except controls were positive for serum HCV RNA. Liver function tests, AFP & CEA levels were assessed. Gene polymorphisms were analysed using PCR-RFLP.

Results: HCC patients had higher G62G (35.4%) and G2 allele (62.5%) of the MMP-1 gene than patients in both cirrhotic groups (P < 0.05) and control groups (P < 0.001). In addition, for the MMP-3 gene, HCC patients had the most noteworthy predominance of mutant 5A/5A (22.9%) and 5A allele (52.1%) compared to the cirrhotic (P < 0.05) and control groups (P < 0.001). The results of MMP-9 gene analysis uncover a higher frequency of the mutant TT genotype and T allele in both HCC (56.3% and 74%) and cirrhotic groups (10% and 35% respectively) compared to the control group. In HCC patients, we detected a significant correlation between heterozygote G1/G2 and G2/G2 of the MMP-1 gene and homozygote TT of MMP-9 with a high CHLD score, tumor size and stage (P < 0.05). Moreover, MMP-3 5A/6A was associated with a higher CHLD score, portal vein thrombosis and stage (P < 0.05) compared to other genotypes.

Conclusions: Gene mutations in MMP-1, 3, 9 may be involved in progression of liver cirrhosis and risk relationship for HCC development.

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Heterogeneity of epigenetic and EMT marks observed in hepatocellular carcinoma with keratin 19 proficiency


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Background: The expression of keratin 19 (K19) has been proposed as a novel predictor for poor prognosis in patients with hepatocellular carcinoma (HCC). However, the cell origin of K19 proficient HCC remains controversial. We tried to reveal the cell origin of K19-proficient HCC by tracing epigenetic footprints in cultured cells and clinical materials.

Methods: The KRT19 gene, which encodes K19, has a CpG island in promoter region and therefore implicates DNA methylation as a potential epigenetic process for K19 expression. Firstly, we examined epigenetic alterations in K19-positive HCC cell lines. Next, from a panel of 564 surgically resected HCCs, we clarified the clinicopathological resectability and K19 proficiency of HCCs by analyzing robust methylation analyses in KRT19 promoter region and LINE-1 in comparison with other cholangiocytic (K7), hepatic cytokeratin (HepPar-1 and Arginase-1), EMT markers (E-cadherin and vimentin), and a signal was assessed with binary differentiation (NOTCH-1).

Results: In vitro, although methylation in KRT19 promoter was associated with K19 deficiency, 5-aza-4c-treatment failed to re-express K19. From 564 surgically resected HCCs, a cohort of 125 HCC patients was selected and analyzed after exclusion of HCC with recurrence, TNM stage as IIIB or more, preoperative therapy, transplantation, and combined hepatocellular-cholangiocarcinoma. In this cohort, K19 expression was found in 29 HCCs (23.2%), and corresponded with poor survival following surgery (P = 0.025) and extraregional recurrence (P = 0.017). Compared with K19-deficient HCCs, the lower methylation level in KRT19 promoter was observed in K19-proficient HCCs (P = 0.001). In addition, HCC with genome-wide hypermethylation in LINE-1 was frequently observed in K19-proficient HCCs (P = 0.0079). Additionally, K19 proficiency was associated with K7 proficiency (P = 0.043), and reduced both E-cadherin and HepPar-1 expression (P = 0.043 and < 0.001, respectively).

Conclusions: K19-proficient HCC showed the poor prognosis owing to extraregional recurrence and the molecular signatures were different from K19-deficient HCC, providing novel insights of heterogeneity underlying development of HCC with extraregional metastasis.

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Rare malignancy rare site: Extranodal lymphomas

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Background: Extranodal Non-Hodgkins Lymphoma (NHL) constitutes one quarter of all NHL cases. Oral cavity and breast represent 2 such uncommon sites.

Methods: Clinical and treatment details of patients with extranodal lymphomas who underwent treatment at our center were collected. Diagnosis was established by excision biopsy or by punch biopsy from the lesion. Histopathological examination (H&E) and immunohistochemistry (IHC) were performed. For staging, patients underwent positron emission tomography (PET) with computed tomography (CT) scan of the whole body.

Results: Case 1: A 32-year old male presented with complaints on the right-side base of tongue and difficulty in swallowing since 20 days. On examination, a nodular swelling was seen over the right side posterior one third of tongue going up to base of tongue. Punch biopsy from the tongue lesion was suggestive of NHL. IHC showed CD-3 – positive, CD 30 – positive, ALK 1 – positive and CD 20 – positive with a final report of anaplastic lymphoma kinase (ALK) positive ALCL. Whole body PET-CT showed localized retropharyngeal uptake in the tongue and in the right cervical lymph node - level II. A final diagnosis of ALK positive ALCL - stage II was made. Case 2: A 22-year old female presented with complaints of lump in the right breast since 10 weeks. On examination there was a lump in the right breast measuring 3.5 x 2 cm in the lower outer quadrant and no other palpable lymphadenopathy. On evaluation, wide local excision of the lump was suggestive of a round cell tumor. IHC done showed the neoplastic round cells to be positive for CD20, PAX5, CD 10 with a Ki 67 of 80% and BCL 2 -1 negative, 5% higher CD 30 positive. PET-CT showed metabolically active sub-centimetric right axillary lymph node enlargement with diffuse hypermetabolism along axial bone marrow.

Conclusions: Only 11 published cases of oral ALCL have been reported. Primary breast lymphoma is a rare disease, accounting for only 0-4.5% of all breast malignancies, 0.3-0.7% of all NHL. Extranodal NHL can occur at any site and keeping an open mind is the most important pre-requisite for making a diagnosis. Modern diagnostic tools such as IHC is mandatory for diagnosis and management of extranodal NHL.

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Descriptive analysis of families with TP53 mutations: Is there a genotype/phenotype correlation?


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Background: Li-Fraumeni syndrome (LFS) is a rare and serious hereditary cancer syndrome caused by germline mutations in the TP53 gene. Our objective is to review the molecular and clinical characteristics of our 64 LFS families.

Methods: Retrospective descriptive analysis. Molecular genetic diagnosis was done either by Sanger or NG Sequencing (Twist Cancer, Illumina); Large Genomic rearrangements were tested by MLPA (MBI, Holland).

Results: Among 4952 non-related families registered in our multidisciplinary program, 395 are BRCAl/2 families and 36 have other molecular diagnoses with 7364 confirmed TP53 families. Twenty-nine pts were reviewed, including 2 male carriers, (36, 40) years that haven’t developed cancers yet. Forty-four pts were registered (median of 1.41 tumours/carrier, IQR: 0–4). Female was 2.1 male. Median age for the first tumour was 24 years (1–45) in the index cases and 35 (15,5–61) in relatives (P = 0.05). Breast cancer (BC) (34% of cancers/48% pts) and sarcoma (31% of cancers/44% pts) were the most common malignancies. For BC cases hormone receptor status was confirmed in 8/14 (positive in 6/8, simultaneous HER2 positivity in 2 cases). Median age of death was 40 (34-58). Most mutations were missense (5 - 2 dominant-negative affecting the DNA binding domain: c.743G>A, p.R248Q and c.725G>A, p.R248Q. One of the missense mutations in LSF. Breast cancer and sarcomas were the most frequent cancers and missense, non-recurrent mutations were mostly observed. In this study c.418G>A, p.A161V; c.86del, p.N29Tfs*15 and c.990del, p.Q331Rfs*14 Chompret criteria were met in 67/3% of cases and didn’t identify a breast cancer only family, with 3 consecutive generations affected.

Conclusions: Our data confirms the heterogeneity and complexity of malignancies and mutations in LSF. Breast cancer and sarcomas were the most frequent cancers and missense, non-recurrent mutations were mostly observed. In this study c.418G>A, p.A161V; c.86del, p.N29Tfs*15 and c.990del, p.Q331Rfs*14 Chompret criteria were met in 67/3% of cases and didn’t identify a breast cancer only family, with 3 consecutive generations affected.

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