

CONGRESS HIGHLIGHTS

MONDAY 19 DECEMBER 2016



Checkpoint inhibitors: Changing the face of NSCLC treatment

Antibodies against PD-1 and PD-L1 are fast becoming integrated into the anti-cancer arsenal. Yesterday's Presidential Symposium featured results from trials investigating agents that look set to change how we treat non-small-cell lung cancer (NSCLC).

The anti-PD-1 antibody, pembrolizumab, is approved second-line treatment for PD-L1-expressing NSCLC. Martin Reck (Lung Clinic Grosshansdorf, Germany) reported results from the first phase III trial (KEYNOTE-024) studying pembrolizumab first line in 305 patients with PD-L1 expression in $\geq 50\%$ of tumour cells (**Abstract 4370**).¹ Compared with platinum-based chemotherapy, pembrolizumab

prolonged progression-free (hazard ratio [HR] 0.50; $p < 0.001$) and overall (HR 0.60; $p = 0.005$) survival and led to fewer grade 3–5 adverse events (27% versus 53%).

The results of the first phase III trial of a PD-L1-targeted drug in NSCLC were presented by Keunchil Park (Samsung Medical Center Sungkyunkwan University School of Medicine, Seoul, Republic of Korea), who discussed the OAK trial in previously treated NSCLC (**Abstract 4380**).² Among the initial 850 patients enrolled, overall survival increased with atezolizumab compared with docetaxel (HR 0.73; $p = 0.0003$); this occurred irrespective of PD-L1 expression and histology.

Atezolizumab in second-line treatment led to a 27% relative reduction in the risk of death compared with docetaxel.

Atezolizumab also had a favourable grade 3–4 treatment-related adverse event profile (15% versus 43%). Professor Park observed: "Atezolizumab offers a new second-line strategy for NSCLC, independent of tumour PD-L1 status."

1. Reck M, et al. *N Engl J Med* 2016;375:1823–33
2. Data first reported at ESMO 2016: Abstract LBA44_PR

"Pembrolizumab should become a standard of care for the first-line treatment of patients with advanced NSCLC and high PD-L1 expression."

Martin Reck

ESMO 2016
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Are we underestimating cancer pain?

The well-recognised adverse effects of cancer pain on patients' quality of life and daily functioning persist in Southeast Asian patients despite the use of analgesia, according to the results of an observational study reported yesterday by Francis Javier (St Luke's Medical Center, Quezon City, Philippines) (**Abstract 5220**). Nearly all of the 462 eligible patients received opioids (91%). While 79% of investigators assessed pain control as being at least 'acceptable', patients' mean (\pm standard deviation) pain intensity was 4.1 ± 2.6 on a scale of 0 (no pain) to 10 (worst pain). Surprisingly, although patient satisfaction with pain control was high (60%), many reported pain/discomfort and functional difficulties.

In a presentation yesterday, Sun Kyung Baek (Kyung Hee University Hospital, Seoul, Korea) encouraged healthcare workers to prioritise relief of background cancer pain (BCP) over breakthrough cancer pain (BTcP) (**Abstract 491P_PR**). In a Korean study of 1,841 patients, moderate or severe BCP was significantly associated with sleep disorder ($p < 0.0001$) and pain control dissatisfaction ($p < 0.0001$) unlike BTcP.

Commenting on the findings, Stefan Zimmermann (HFR Fribourg-Hôpital Cantonal, Switzerland) said: "Pain is still feared by cancer patients as one of the most prevalent symptoms." Two-thirds of patients with advanced cancer experience pain and numerous studies highlight significant under-treatment. "Both studies deliver a clear message: that effective pain management—and especially BCP—is a key element in securing improvements in quality of life, overall symptom control and cancer therapy adherence in our patients," he added.

ESMO Asia 2016: Our personal highlights

Pembrolizumab: Cost-effective in Hong Kong for advanced melanoma

The KEYNOTE-006 trial demonstrated the survival benefit of pembrolizumab over ipilimumab in advanced melanoma.¹ A new analysis, presented yesterday, showed that first-line pembrolizumab is also a cost-effective treatment option in Hong Kong (**Abstract 4050**).

The main outcome of the analysis, which was based on data from KEYNOTE-006 and additional sources for other comparators, was the incremental cost-effectiveness ratio (ICER) in US dollars (USD) per quality-adjusted life years. According to Herbert Loong (The Chinese University of Hong Kong, China) who presented this abstract on behalf of his co-authors, the ICER for pembrolizumab was USD 8,034 versus ipilimumab and USD 53,123 versus dacarbazine. Comparisons with temozolomide and paclitaxel-carboplatin gave similar results to those versus dacarbazine. The values for all comparisons fall well within the World Health Organization cost-effectiveness threshold, which, at three-times the gross domestic product per capita, is currently USD 119,274 for Hong Kong.

“Checkpoint inhibitors have been game-changers in the treatment of advanced melanoma and this is the first cost-effectiveness study of a checkpoint inhibitor in this setting in the territory,” explained Dr Loong. “We have shown that although the cost of pembrolizumab is significantly more than traditional cytotoxics and somewhat comparable with ipilimumab, the potential benefits in Quality-of-Life Years gained versus these two comparators make first-line pembrolizumab a cost-effective option. We hope that the healthcare funding authorities in Hong Kong will take these data into account when making decisions on drug reimbursements,” he added.

1. Robert C, et al. *N Engl J Med* 2015;372:2521–32

Financial constraints lead to reduced access to cancer medicines

There is mounting evidence that many cancer patients experience financial hardship, partly because many drugs available to patients are not funded by governments, leading patients to pay for their own treatment. This morning's session will feature new data to add to existing information and promises to offer a highly interesting discussion on the problems faced by patients when trying to access cancer drugs.

Don't miss the Special Session, Access to medicines: A global policy issue, 09.00 – 10.45, Room 325

In this final edition, we share with you the *Congress Highlights* Editorial Team's selection of the best bits from the scientific programme. Since we are in an era of immense research activity involving targeted agents, it is somewhat predictable that our selection focuses on this type of therapy.

Giuseppe Curigliano (Editor-in-Chief): For me, some of the most exciting data were in the non-small-cell lung cancer (NSCLC) setting, in which anti-PD-1/PD-L1 antibodies are helping us make huge strides in the management of the disease. KEYNOTE-024 results showed extended progression-free and overall survival for pembrolizumab compared with platinum-based chemotherapy in the first-line treatment of NSCLC (**Abstract 4370**). Also, atezolizumab treatment led to a 27% relative reduction in the risk of death versus docetaxel in previously treated patients with NSCLC in the OAK study (**Abstract 4380**). There was also positive news from a subgroup analysis of the MONALEESA-2 study of first-line ribociclib (a CDK4/6 inhibitor) plus letrozole, in which Asian patients with hormone receptor-positive breast cancer were confirmed to achieve the same benefit as a Western population in terms of progression-free survival (**Abstract LBA1_PR**). This is an important achievement in metastatic breast cancer treatment. Another subgroup analysis—this time from KEYNOTE-012—showed that Asian patients with recurrent and metastatic head and neck cancer had better overall survival and disease control outcomes with fixed-dose pembrolizumab than a mixed-race population (**Abstract 3590_PR**).

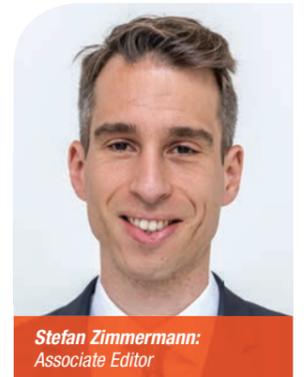
Stefan Zimmermann (Associate Editor): A stand-out presentation for me was the early-phase study of erlotinib combined with the anti-PD-L1 antibody, atezolizumab, in patients with NSCLC harbouring mutations in *EGFR*



Giuseppe Curigliano:
Editor-in-Chief



Markus Joerger:
Associate Editor



Stefan Zimmermann:
Associate Editor

(**Abstract 4410**). This combination is feasible and does not appear to lead to pneumonitis, and the results are particularly relevant for Asian patients with advanced NSCLC, in whom this genetic alteration is very common. While patients with *EGFR* mutation-positive NSCLC have benefited immensely from advances in targeted therapy, they have distinctly lower response rates to PD-1/PD-L1 immune checkpoint blockade, particularly among the overwhelming majority whose tumours lack PD-L1 expression. Early trials investigating combinations of *EGFR* TKIs and immunotherapy have been halted because of toxicity, such as pneumonitis with osimertinib-durvalumab. The present good news paves the way for potentially including immunotherapeutic agents early on in the treatment sequence, so that these patients are not excluded from the real hope raised by immunotherapy: namely, long-term tumour control that is not achievable with targeted therapies alone.

Markus Joerger (Associate Editor): Of all the developmental drug presentations, the most prominent and appealing for me has to be the results for the first-in-class pan-Trk inhibitor, LOXO-101, showing high activity in tumours harbouring *NTRK* gene fusions. In the study, 6 of 7 evaluable patients had confirmed RECIST

responses, with all 7 having tumour regression (**Abstract 1500**). Although not strictly speaking a developmental agent, the Claudin18.2-directed antibody, IMAB362, was shown in the FAST study to extend progression-free and overall survival when combined with first-line EOX chemotherapy in patients with advanced gastric cancer (**Abstract 2200**). Claudin18.2 is a tight junction protein abundant in certain gastric and intestinal cancers, and possibly because of IMAB362's target and mechanism of action, vomiting was a common side effect in the study. Further research is likely to combine the antibody with a less emetogenic chemotherapy regimen in an attempt to reduce such effects. Lastly, there was promising news for the *EGFR*-targeting, first-in-class antibody-drug conjugate, ABT-414, when combined with temozolomide in patients with recurrent glioblastoma (**Abstract 1380**). *EGFR* is amplified in around half of glioblastoma patients and few therapeutic options exist: prognosis is usually very poor. In a study of 51 patients, an objective response rate of 8.7% was reported, with 46% having stable disease. Further investigation is no doubt warranted.

We hope you have enjoyed catching up on all the news from ESMO Asia 2016. Thank you for taking the time to read the *Congress Highlights* and we look forward to seeing you next year!

Right-sided disease is not negatively prognostic in *KRAS*-mutated colorectal cancer

Mounting evidence points towards right-sided disease being a negative prognostic indicator in colon cancer. Supporting data include analyses from the recent ASCO and ESMO congresses,^{1,2} which were restricted to patients with *KRAS* wild-type (*KRAS*_{wt}) disease. Results from a retrospective analysis presented yesterday by Radka Obermannova (Masaryk Memorial Cancer Institute, Brno, Czech Republic) suggest that the prognostic effect is lost in patients with *KRAS*-mutated (*KRAS*_{mt}) colon cancer (**Abstract 1680**).

According to prospectively collected National Czech Registry data from 1,047 patients, primary tumours were right-sided, left-sided and rectal in 26.8%, 41.1% and 32.1% of patients, respectively. Of 88.8% patients with known *KRAS* mutation status, half had *KRAS*_{wt} and half *KRAS*_{mt} disease. For the whole population, overall survival (OS) and progression-free survival (PFS) were prolonged in left- versus right-sided disease. However, among patients with

*KRAS*_{mt} disease, there were no significant differences between right- and left-sided disease in either OS (hazard ratio [HR] 1.19; 95% confidence intervals [CI] 0.90–1.58; *p*=0.231) or PFS (HR 1.06; 95% CI 0.83–1.36; *p*=0.653).

In *KRAS*-mutated colorectal cancer, overall and progression-free survival were similar for right- and left-sided disease.

“Further studies are needed to reveal the potential therapeutic impact of prognostic differences in left- versus right-sided disease,” comments Markus Joerger. Giuseppe Curigliano adds, “Extensive whole genome analysis should uncover any biological variations in between left- and right-sided disease, which will help to refine treatment by identification of potential new targets.”

1. ASCO 2016; www.ascopost.com/News/40569

2. Abstract 89P, ESMO 2016; www.esmo.org/content/download/88721/1622334/file/ESMO-2016-abstracts-excl-LBA-and-press-programme.pdf



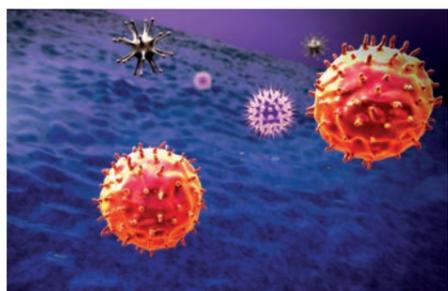
ESMO-WHO

Special session on tobacco and cancer

The session this morning will outline the latest evidence from the WHO on tobacco use and cancer treatment, highlighting the importance of smoking cessation programmes. You'll also find out how an ESMO-WHO partnership is assisting clinicians to help their patients.

Don't miss the Special Session, Tobacco use and cancer treatment, 11.00 – 12.30, Room 336

Tomorrow's treatments? Novel anti-cancer agents at ESMO Asia 2016



The search for new anti-cancer drugs never stops. Here we highlight just a few of the promising agents in early-stage development featured at this year's ESMO Asia Congress.

On Saturday, a phase Ib dose-escalation study, reported by Takashi Ura (Aichi Cancer Center Hospital, Nagoya, Japan), demonstrated that adding the *EGFR*-targeted monoclonal antibody, nimotuzumab, to cisplatin-5-fluorouracil-based chemoradiotherapy for the treatment of 10 Japanese patients with stage II-III oesophageal cancer led to a complete response rate of 50% and a 1-year survival rate of 75% (**Abstract 235P**). Grade >3 haematological toxicities were common but there were no treatment-related deaths and no grade ≥3 skin toxicity. A change in the producer's development strategy prevented further dose escalation of nimotuzumab.

The first-in-class antibody-drug conjugate ABT-414 targets *EGFR*-amplified tumours, delivering a potent microtubule cytotoxin. In another presentation on Saturday, Martin van den Bent (Erasmus MC Cancer Institute, Rotterdam, Netherlands) reported encouraging activity with a combination of ABT-414 and temozolomide in 51 patients with *EGFR*-amplified, temozolomide-refractory glioblastoma (**Abstract 1380**).

58% of patients largely with temozolomide-refractory glioblastoma achieved a partial response or stable disease with ABT-414 plus temozolomide.

Sunday's Developmental Therapeutics Proffered Paper Session included reports from two phase I dose-escalation studies in patients with solid tumours. Todd Bauer (Sarah Cannon Research Institute/Tennessee Oncology, Nashville, Tennessee, USA) discussed the orally administered, selective, pan-Trk inhibitor LOXO-101 (**Abstract 1500**). Among 59 patients treated, 6 of 7 patients with *NTRK* fusion gene-positive tumours who were eligible for efficacy assessment had a partial response; 7 others continue to receive LOXO-101 (range 2–22 cycles). Later in the Session, Vincenzo Teneggi (A*STAR, Singapore) reported first-in-human results with the selective Wnt signalling pathway inhibitor, ETC-159, showing successful target inhibition and no treatment-related serious adverse events or dose-limiting toxicities (**Abstract 1520**).

Some of these agents have exceptional clinical potential. For example, if nimotuzumab's efficacy were to be confirmed in an expansion cohort, this drug could change practice for the treatment of locally advanced oesophageal cancers. Also, the future of ABT-414 is unquestionably promising, given that 50% of glioblastomas harbour *EGFR* amplifications and there is currently no second-line standard of care.

Immunotherapy prolongs survival for gastric cancer patients

Claudin18.2 is a tight junction protein that is expressed in a high proportion of gastric cancers.¹ The first-in-class Claudin18.2-directed antibody, IMAB362, significantly improves survival when added to standard first-line treatment with epirubicin, oxaliplatin and capecitabine (EOX) for advanced gastric and gastroesophageal junction (GEJ) cancers.

Hear the full presentation of the randomised FAST trial in today's Proffered Paper Session on Gastrointestinal Tumours (11.00 – 12.30, Hall 405, Abstract 2200).

Florian Lordick (University Cancer Centre Leipzig, Germany) will present data showing that among 161 patients with Claudin18.2-expressing tumours (immunohistochemistry-detected expression ≥2+ in ≥40% tumour cells), IMAB362 plus EOX prolonged progression-free survival (PFS) (hazard ratio

[HR] 0.47; $p=0.0001$) and overall survival (OS) (HR 0.51; $p=0.0001$) compared with EOX alone. Higher Claudin18.2 expression led to better PFS (HR 0.36) and OS (HR 0.45).

Commenting on the findings, Markus Joerger (Cantonal Hospital, St. Gallen, Switzerland) said that data from the FAST trial open new treatment opportunities for patients with GEJ cancers. "It is uncommon to observe an improvement in OS in these patients," he said, "but the combination of chemotherapy and IMAB362 offers a new and potent treatment option for up to 70% of patients with advanced gastric or GEJ cancers; tumours that have been hard to treat and for which no substantial improvements have been seen for many years." Claudin18.2 is only the second clinically actionable biomarker in gastric cancer, following *HER2/neu* immunohistochemical expression. In the future, IMAB362 may also be explored in these patients in the neoadjuvant and adjuvant setting.

1. Sahin U, et al. Clin Cancer Res 2008;14:7624–34

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| IMPORTANT DEADLINES | |
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| 12 July 2017 | Abstract submission |
| 23 August 2017 | Early registration |
| 11 October 2017 | Late-breaking abstracts |
| 11 October 2017 | Late registration |

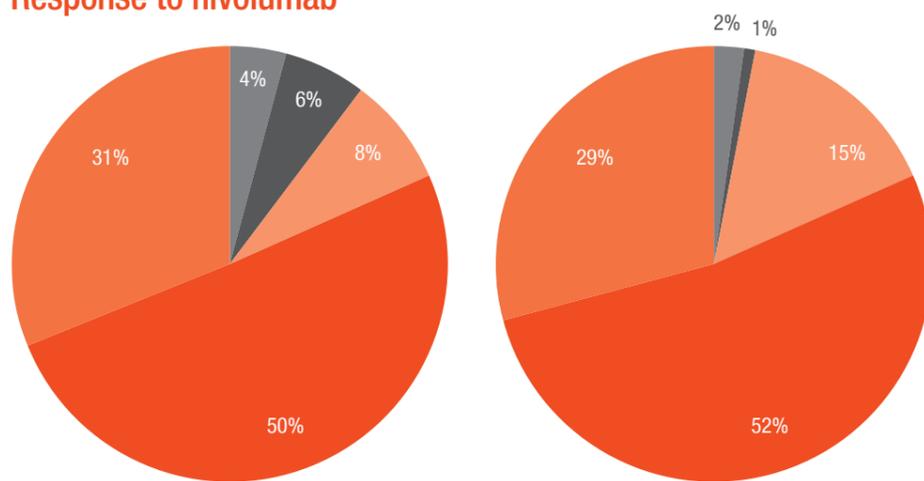
Encouraging activity with nivolumab in hepatocellular carcinoma

Survival times for patients with advanced hepatocellular carcinoma (aHCC) failing sorafenib are only approximately 7–8 months. The anti-PD-1 antibody, nivolumab, is showing potential in this setting, according to an interim analysis of the phase I/II CheckMate-040 study being presented today by Ignacio Melero (Clinica Universidad de Navarra and CIBERehd, Pamplona, Spain) (**Abstract 2190**).

Patients with aHCC received nivolumab in three dose escalation cohorts (0.1–10 mg/kg)—hepatitis

B virus (HBV)-infected, hepatitis C virus (HCV)-infected and uninfected—and four expansion cohorts (3 mg/kg)—uninfected sorafenib-naïve/intolerant, uninfected sorafenib progressors, HBV- and HCV-infected. In the expansion cohort, 65% of patients had treatment-related adverse events (18% grade 3–4), the most common being fatigue (21%), pruritus (15%), rash (12%) and diarrhoea (9%). Responses (see figure) were independent of HCC aetiology and PD-L1 expression.

Response to nivolumab



Dose escalation phase (n=48)

Expansion phase (n=214)

■ Stable disease ■ Progressive disease ■ Partial response ■ Complete response ■ Not evaluable

Get all the results in today's Gastrointestinal Tumours Proffered Paper Session: 11.00 – 12.30, Hall 405.



A new molecular screening programme in Asia aids personalised treatment

Multi-marker molecular cancer screening is key to targeting treatment but data are lacking in Asia. Findings from one of the first precision oncology protocols to be initiated in Asia, the Integrated Molecular Analysis of Cancer (IMAC), were discussed yesterday by Nicholas Syn (National University Cancer Institute, Singapore [NCIS]) (**Abstract 1490**).

Next-generation sequencing was possible in 365 (92%) of 396 patients with advanced/recurrent malignancies. Reportable mutations were found in 82% of these patients and potentially actionable mutations were seen most commonly in *PIK3CA*, *KRAS* and *PTEN*. Mutations were also observed in *TP53*. Twenty-three patients were enrolled in matched biomarker-enriched clinical trials, with 45% of 20 evaluable patients achieving a clinical benefit for ≥ 8 weeks.

The NCIS IMAC protocol is feasible for therapeutic prioritisation and shows early evidence of clinical benefit.

Commenting on the significance of these findings, Markus Joerger (Cantonal Hospital, St. Gallen, Switzerland), said that molecular profiling of cancer patients is important to enable treatment with molecularly-targeted agents. "Investigators as well as patients must be aware, though, that even in the largest centres, usually only 10% to 15% of all patients screened will be eligible to receive molecularly-targeted anti-cancer treatments. The hope is that more somatic mutations will be targetable in the future as our knowledge of tumour biology and pharmacological intervention increases over time," he added.

Nanoliposomal irinotecan: A new standard of care for metastatic pancreatic cancer in Asian patients

The survival benefit of nanoliposomal irinotecan (nal-IRI) for patients with metastatic pancreatic cancer previously treated with gemcitabine was established in the phase III NAPOLI-1 trial.¹ A new subgroup analysis has now confirmed that this advantage extends to Asian patients.

Among 132 Asian patients, the combination of nal-IRI plus 5-fluorouracil/leucovorin (5-FU/LV) improved median overall survival compared with 5-FU/LV alone (8.9 months versus 3.7 months; $p=0.0281$), according to Li-Tzong Chen (National Health Research Institutes, Tainan, Taiwan), who presented the data yesterday (**Abstract 221PD**).

Adding nal-IRI to 5-FU/LV prolonged survival by 5.2 months.

The incidence of grade ≥ 3 neutropenia (55% versus 2%) and decreased white blood cell count (21% versus 0%) was higher for nal-IRI plus 5-FU/LV than 5-FU/LV alone, but there was no grade ≥ 3 peripheral neuropathy. These findings were consistent with the results in the overall population of the NAPOLI-1 study and confirm the effectiveness and manageable tolerability of nal-IRI plus 5-FU/LV in Asian patients with metastatic pancreatic cancer.

1. Wang-Gillam A, et al. *Lancet* 2016;387:545–57

Don't let cytogenetics take a back seat in CML



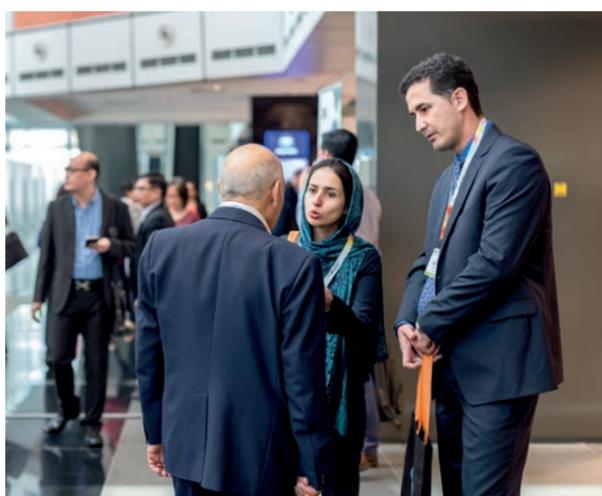
The prognostic impact of individual additional cytogenetic aberrations (ACAs) has not been shown. Dr Madhav will present survival outcomes for 92 patients with ACAs at diagnosis or progression who were stratified into three groups: 1. Trisomy 8, lack of Y chromosome, additional Ph chromosome, trisomy 19 and increased ploidy; 2. Monosomy 7, *i(17)(q10)*, 3q rearrangements, two or more ACAs and hypoploidy; 3. Minor route ACAs.

Overall survival was significantly better in patients without ACAs than those with ACAs.

Danthala Madhav (Nizam's Institute of Medical Sciences, Hyderabad, India) will today urge physicians not to overlook the importance of cytogenetic testing in chronic myeloid leukaemia (CML) (Haematological Malignancies Proffered Paper Session: 09.00 – 10.48, Room 336, **Abstract 3340**).

The findings highlight that risk stratification based on an individual ACA's prognostic relevance may be a useful alternative to simply categorising ACAs into major and minor route abnormalities for assessing prognosis and guiding treatment.

Faces in the crowd



Impact of surgery on survival and quality of life: More data in breast cancer

Two presentations in today's Breast Cancer Poster Discussion Session from investigators at Seoul National University Bundang Hospital, Korea, highlight different, but equally important aspects related to surgery in the field of breast cancer.

Surgery led to a 90-month improvement in survival (118 months versus 28 months, $p<0.001$).

Find out more today! 09.00 – 10.00, Summit 2.

Hye Jin Kim will report that surgical removal of the primary tumour in patients with stage IV breast cancer significantly improves survival (**Abstract 117PD**). In a retrospective review of 157 patients, only surgery ($p<0.001$) and response to chemotherapy ($p=0.042$) were independent predictors of survival.

The impact of risk-reducing salpingo-oophorectomy (RRSO) on quality of life (QoL) in *BRCA* mutation carriers will be discussed by Yerang Jang (**Abstract 67PD**). The post-surgical QoL of 26 patients undergoing RRSO was not significantly different from that of 19 patients not receiving RRSO. Among RRSO patients, the only significant QoL change after surgery was an improvement in physical QoL ($p=0.004$).

ESMO would like to thank the *Congress Highlights* Editorial Team, Editor-in-Chief Giuseppe Curigliano and the Associate Editors Markus Joerger and Stefan Zimmermann, and TMC Strategic Communications, for all their hard work in bringing you the news from ESMO Asia 2016. Covering an important Congress was a challenge and the team spent many hours debating what would be of most interest to you. We hope you agree that the team did a fantastic job in capturing the essence of the ESMO Asia 2016 Congress and in highlighting the many important sessions that took place.

