ESMO Research Research Fellowship
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FINAL REPORT

Host Institute: **Vall d'Hebron Institute of Oncology, Barcelona, Spain.**
Mentors: **Dr. Joaquin Mateo and Dr. Rodrigo Dienstmann**
Project title: **Integration of genomic testing and patient expectations into prostate cancer treatment decision-making**

Home Institute: **Ángel H. Roffo Oncology Institute, Faculty of Medicine, University of Buenos Aires; Buenos Aires, Argentina.**

Introduction

Precision medicine is changing the approach to cancer treatment. In metastatic prostate cancer, the approval of PARP inhibitors represents the first-ever biomarker-driven treatment, advocating for the incorporation of genomic testing into patients' journeys.[1] Metastatic prostate cancer is a lethal disease, showing heterogeneous molecular profiles enriched for alterations in AR, TP53, RB1, PTEN, Wnt/B-catenin, and DNA damage response (DDR) pathways, sometimes with genetic germline alterations.[2,3] Currently, in the hormone-naïve prostate cancer (HNPC) setting androgen deprivation therapy (ADT) combinations with androgen-receptor signaling inhibitors (ARSI) or taxanes have proved to delay the evolution towards metastatic castration-resistant prostate cancer (mCRPC) improving patients' outcomes.[4-6] However, there are no tools to identify the best of these options for each patient. Moreover, the first therapy chosen will induce tumor-selective pressure impacting mCRPC development and, potentially, response to further treatments.
In this project, I will use a liquid biopsy assay to correlate patients' outcomes with the genomic landscape of mCRPC after HNPC treatment. Considering the challenges of interpreting genomic results in daily clinical practice, I will establish a decision support tool for the exploration and interpretation of genomics data that combines clinical features, facilitating multidisciplinary tumor board discussions and treatment planning. Besides treatment selection and genomic result interpretation, precision oncology poses communication challenges.[7] Oncologists need to discuss complex biological information with patients, balancing patient expectations and clinical uncertainties. Considering the gap in knowledge about the patient experience passing through genomic testing,[8] I will pursue a study of patients' expectations regarding genomic profiling in prostate cancer.

Rationale and Aim

Aim 1.- *To study metastatic castration-resistant prostate cancer (mCRPC) genomic profiles and to correlate them with patients' outcomes, considering the prior therapy in the HNPC setting: androgen deprivation therapy (ADT) alone vs ADT + docetaxel vs ADT + androgen-receptor signaling inhibitors (ARSI).*
Prostate cancer is a genomic heterogeneous disease. Different genomic profiles have been identified and linked with prognosis and treatment response. First-line therapies, such as ADT, ARSI, or taxanes, can delay the progression to the mCRPC setting, but inevitably they induce a selective pressure impacting the genomic disease evolution. There are no tools to prioritize one of these treatment options for each patient, and the current information about the genomic patterns of these subsets of patients is insufficient. Therefore, the study and

identification of specific genomic profiles involving each of these subgroups will contribute to the clinical implementation of precision medicine in prostate cancer following a patient-centric approach, potentially impacting how to design further therapeutic strategies.

Aim 2.- *To deploy a clinical informatics platform for visualization and exploration of clinico-genomics data as a decision support system in prostate cancer.*
The organization of genomic data, their joining with clinical information, and finally, the access, visualization, and exploitation of all these data create complex challenges. Moreover, the high dimensionality of the data and the complexity of their relationships pose difficulties in their implementation in daily clinical practice. Hence, it is key to develop an interactive decision support tool for clinico-genomics data analytics in routine patient care, facilitating their interpretation and discussion in multidisciplinary tumor boards and treatment planning.

Aim 3.- *To evaluate the expectations of prostate cancer patients undergoing genomic testing, before the test and after the communication of results.*
Precision oncology and the implementation of genomic testing create communicative challenges and impact the patient journey. Currently, there is scarce information about patients' understanding of genomic testing and how they pass through this experience. Assessing patients' perspectives and expectations when facing genomic testing will allow an understanding of the patient experience to finally deliver patient-centered care respecting the individual patient's preferences, needs, and values.

Experimental design

Aim 1.
To understand the genomic profiles of patients after the first line of therapy, a liquid biopsy of three cohorts will be studied according to the treatment received in the HNPC setting: those treated with ADT alone, those who received ADT+ARSI, and those with ADT+docetaxel. Genomic profiles will be characterized and analyzed from circulating tumor DNA after the first line of therapy, besides, they will be compared with genomic patterns found in tumor samples before starting the first line. Considering the slow accrual rate and the low number of progress events, particularly, in the ADT+ARSI cohort; we redesigned this aim into two sequential steps. The first one was planned as an exploratory analysis based on external datasets, and the second one was designed to refine and validate the results in the original Vall d'Hebron Institute of Oncology (VHIO) cohort.
Methodology- *Objectives:* (i) to analyze and compare genomic profiles of these three subsets; (ii) to compare genomic profiles of each subgroup before and after the first line in HNPC; (iii) to explore mechanisms of treatment resistance according to the genomic selective pressure; (iv) to explore the existence of actionable mutations. *Study design:* considering the two sequential steps, we planned to analyze external databases to identify a potential set of alterations and genomic profiles. Then, these alterations and features would be validated in our local cohort, leveraging the detailed clinical information collected for this population in our center. To pursue this second step, samples and data were planned to be collected upon an observational prospective study headed by Dr. Mateo and designed for the acquisition of longitudinal samples (blood and tumor biopsies) and clinical data from patients receiving treatment at the Vall d'Hebron University Hospital (VHUH) (PRO-5248). The sample size for each cohort was: ADT alone, n=30; ADT+ARSI, n=55; ADT+docetaxel, n=55.

Contingency plan- In line with the aim of improving the understanding of prostate cancer genomics, a project was designed to evaluate the homologous recombination repair (HRR) status with a multi-omics approach, including gene-level alterations, genomic scars, transcriptomics, and the functional RAD51 immunofluorescence based (RAD51-IF) assay. *Study design:* Leveraging the observational study led by Dr Mateo at VHUH (PRO-5248), a retrospective analysis was planned to pursue a comprehensive characterization of HRR deficiency (HRD) in a real-world population with metastatic prostate cancer (mPC). The RAD51-IF is a novel assay looking at the formation of nuclear RAD51 foci which has been identified as a marker of HRR proficiency. In addition, samples

were analyzed with low-pass Whole Genome Sequencing (lpWGS), Whole Exome Sequencing (WES) or targeted panel (Panel), RNAseq, and the RAD51-IF assay. Genomic scars, such as LST, LOH, NtAI, and the unweighted sum (HRD-sum), were calculated from WES or Panel; besides, LGA was obtained from lpWGS. Clinicopathological data and treatment information were explored in search of meaningful associations, as well as to study the prognostic role of the RAD51-IF.

Aim 2.
To facilitate genomic data visualization and interpretation, a customized version of cBioPortal will be designed and implemented at VHIO. cBioPortal allows linking genomic and clinical data, providing insight at both levels, at the large cohort scale and the individual patient level. The interactive platform allows filterint, exploring, analyzing, and visualizing sets of relevant variables whilst it can control the accessibility with a user and password system.
Methodology- *Objectives:* (i) to install and implement the cBioPortal platform at VHIO; (ii) to test the platform requirements with a first pilot project combining genomic and clinical data of prostate cancer; (iii) to establish the workflow and pipelines according to the cBioPortal requirements; (iv) to integrate cBioPortal as a tool to visualize and analyze genomic and clinical data for prostate cancer research projects. *Project design and plan:* clinico-genomics information of prostate cancer patients was used considering a prior project PRO-5248. Data for this project have been collected and curated, and are maintained in SQL databases and REDCap. To complete the first two objectives, all the data had to be curated and structured according to the platform's requirements. Three main goals were defined to complete this stage: (a) the clinical data revision and curation; (b) standardization of the genomic data; and finally (c) customization of the cBioPortal version to VHIO. Then, during the second stage, considering the implementation in ongoing prostate cancer projects, the workflow was defined and the final customization was performed.

Aim 3.
This aim was planned to be pursued through two consecutive studies. First, a pilot local study at VHIO aimed to gather the first results about prostate cancer patients' expectations under genomic testing, before the test, and after the communication of the results. Secondly, these results and findings were planned to be leveraged in the second analysis conducted in a multicenter study designed to evaluate the feasibility and impact of liquid biopsy-based genomic testing on treatment decision-making in metastatic prostate cancer patients.
Methodology- First step. *Objectives:* (i) to develop an experience evaluation tool; (ii) to evaluate prostate cancer patients' experience during genomic testing, before and after pursuing the test; (iii) to analyze the performance of the questionnaire developed; (iv) to describe the findings obtained. *Study design:* prostate cancer patients who are enrolled in an ongoing prospective genomic study (PRO-5248) at VHIO were invited to participate. An experience evaluation tool was built to assess patients' expectations, concerns, and attitudes regarding genomic testing. This tool was implemented before and after pursuing the genomic testing.

Second step. *Objectives:* (i) to complete the development of the experience evaluation tool; (ii) to validate the strategy and questionnaires developed to measure and characterize patients´ experience; (iii) to describe patients´ knowledge, concerns, and expectations in the pre-genomic testing setting; (iv) to describe the fulfillment of their concerns and expectations after the communication of the genomic results. *Study design:* This study (SOLTI-2102-HOPE-Prostate) is part of a SOLTI Foundation project, designed to assess the impact of liquid biopsy-based genomic profiling on treatment decision-making for patients with metastatic prostate cancer in Spain. In this study, patients take the lead in participation and data self-reporting, as opposed to the classical approach of centering research in hospitals and investigators. Patient registration, consent, and screening are articulated through a web-based tool; once enrolled, patients donate blood samples through a network of community laboratories in Spain, which send the blood and (when available) tumor tissue samples to the central laboratory at VHIO. At this point, before the implementation of the genomic testing, patients receive the previously designed questionnaires through an online platform. After discussing their genomics results in a virtual tumor board, a report with a "clinical interpretation" summary is shared with the patient and treating physician. Patients then receive the post-test questionnaire and every 6 months receive a follow-up questionnaire to record if any therapeutic action was taken on the genomics data. Regarding the statistical analysis to explore and define the

final set of items to be included in the experience tool, several steps were pursued. First, a descriptive analysis was performed to evaluate the answers' variability, discrimination capacity, and metrics related to the global performance such as the Guttman's lambda 6, the correlation with the total score, and the Cronbach's α coefficient when the item is dropped. The Omega and Cronbach's α coefficients were used as a reliability measure of internal consistency, representing the estimation of the general factor saturation of a test. Secondly, an Exploratory Factor Analysis (EFA) was implemented to define the ultimate list of items as well as their relationship with each domain. The EFA is a commonly used unsupervised statistical technique to identify the relative importance of each item and how they are associated with a construct (domain). Regarding the post-genomic testing questionnaire, while the items for each domain were not identical to those in the pre-questionnaire; each one from the post- was related to the corresponding item in the pre-questionnaire. Therefore, items excluded from the pre- were excluded from the post-questionnaire as well. Through this sequential process, iteratively, the final list of items was created; first, in the local pilot study and then, in the multicenter project. For the statistical analysis and the experience evaluation tool development, I have received the additional mentoring of Jesica Formoso from Argentina (Centro Interdisciplinario de Investigaciones en Psicología Matemática y Experimental - CONICET).

Results, Conclusions, and Future Perspectives

Aim 1.

Considering the redesign of this aim into two sequential steps, we planned to interrogate databases from Foundation Medicine and GENIE. After several queries throughout the length of the project, Foundation Medicine did not find a sufficient number of patients that progressed upon ARSI+ADT. Therefore, during year 2, we contacted with GENIE Consortium, although they have tissue samples the information acquired could be useful as well. We designed the Data Analysis Plan and a project summary, required to have access to the data, and our aim overlapped with some of their ongoing projects. Thus, we went through several meetings to design a collaboration plan. As a result, they recently gave us access to the complete database with genomic and clinical data (n=1116). Unfortunately, there is still a lower number of patients in the ARSI+ADT group (n=41); even more scarce, since this cohort was planned as an exploratory analysis due to the retrospective nature of this database. Therefore, the alternative approach under consideration is to analyze all the samples collected after ARSI in the mCRPC setting to identify a general genomic landscape; and then, to explore the small set in the HNPC scenario. Hoping to then validate those findings in our local cohort.

Regarding the longitudinal study, the enrollment of patients and follow-up are still ongoing. The ADT group has completed the recruitment with 30 patients included with all the samples at progression collected. A total of 33 patients were included in the ADT+Docetaxel group, with 26 samples collected and 7 patients under follow-up. Finally, in the ADT+ARSI group, there are 33 patients enrolled, 6 already progressed being their samples collected. For all the patients, the data were collected, revised, and curated by implementing a REDCap platform. Furthermore, several samples were processed and libraries prepared (ADT group, n=18/30; ADT+Docetaxel group, n=13/26; ADT+ARSI group, n=1/6).

Further steps: we acknowledge that the recruitment and the sample collection at progression, especially, for the ARSI+ADT cohort was considerably lower than was expected when the proposal was designed; and as a result, this aim could not be achieved. Nevertheless, different approaches and efforts were conducted to obtain other databases to complement our analysis. At present, since I will continue my work as a researcher in the Prostate Cancer Translational Research Group as well as in the ODysSey Group, and having already established a collaboration with the GENIE Consortium, we plan to analyze these data exploring the genomic effects of ARSI treatment even when they were administered in the castration-resistant setting. Besides, we expect to obtain more samples and results from our local cohort during the following months.

With regard to the second project proposed, all the samples were collected and processed, and the data were analyzed. The result of this project, which I co-lead, is a manuscript already available in bioRxiv (10.1101/2024.01.28.577367) [See below, Ref 1] and prepared for submission to JCI (co-first author); besides, an abstract has been submitted to ASCO congress (first author) [Abstract Ref 1].

In this study, 219 tumor tissues from 187 patients were acquired, including primary (151/219) and metastatic (68/219) cases. Samples were collected either in the HNPC (169/219) or CRPC (50/219) setting. Out of these 219 samples, genomic profiling was obtained for 181 (Panel n=139, WES n=80, both n=38). For those cases where both genomic testing results were available, WES information was prioritized. Gene alterations were common in TP53 (40%), PTEN (14%), AR (15%), MYC (10%), BRCA2 (9%), ATM (8%) and BRCA1 (2%). Tissue for RAD51-IF was available for 206 samples; of those, 140/206 (68%) were considered evaluable for RAD51-IF according to the assay criteria. The median RAD51-IF score for the whole cohort was 28.5. Considering a predefined threshold for RAD51-IF, where samples with <=10% are considered as HRD, 21% of the samples were classified as HRD. No RAD51-IF score differences were seen between primary/metastatic tumors (p=0.7) nor HSPC/CRPC (p=0.49). The sample matched RAD51-IF and genomics data were obtained for 128 biopsies (117 patients).

BRCA1/2 alterations associated with lower RAD51-IF scores (median 3.5, IQR 1.3 – 9.8 for BRCA1/2 altered vs median 29.7, IQR 19.0 - 44.5 for BRCA1/2-WT), resulting in high sensitivity (71%) and specificity (85%) to identify cases with BRCA1/2 alterations. Similar results were obtained, when a larger set of HRR genes was analyzed, sensitivity 68% and specificity 87%.

RAD51-IF was able to classify as HRR proficient BRCA1/2 altered cases after secondary resistance to platinum or with retained BRCA1 expression by IF. Based on HRD-sum and considering the threshold of >=42 to define a sample as HRD, 27.5% and 20.1% cases were classified as HRD according to results from WES and Panel, respectively. CRPC samples were more likely to be classified as HRD-sum "high" (OR 4.07 WES, OR 5.21 targeted panel) HRD-sum was significantly associated with BCRA1/2 (Panel, p= 0.004; WES, p=0.002), and with RAD-IF low for Panel (p=0.021) and for WES once adjusted by castration-sensitivity status (p=0.03).

Treatment information was studied to evaluate the prospective association between RAD51-IF results and clinical outcomes. Nevertheless, as samples were obtained at different time points and the presence of numerous confounding factors, no conclusive results were obtained. Similarly, RNAseq was studied in a small subset of these patients, but the bach effect, the sample origin, and the different time points introduced excessive noise and no clear conclusions could be derived.

Aim 2.

As a result of the project design and plan, and the ongoing longitudinal study PRO-5248, the first stage was the building of a complete database with detailed and curated clinical data. While the whole structure of the REDCap database was already available at the start of the project as well as most of the clinical data belonging to the first 241 cases, I worked actively from the very beginning to improve the database. The first step was to reorganize the structure and the REDCap instruments to improve data quality and collection. Then, a thorough revision and data curation process was performed, including new cases subsequently added. Implementing an automatization process based on R, all the samples collected were labeled according to the treatment time point and the line of therapy. Hence, the first result of the project has been a redesign and complete REDCap database; which has, at present, 312 patients.

Concurrently, we set the bioinformatics workflow and the file requirements (structure, optional and compulsory variables) establishing a work protocol. Thus, we defined and standardized the bioinformatics outputs and the clinical data files. Genomic and clinical data from the prostate projects are in cBioPortal. According to the different sources of genomic data, sequencing information is available through targeted panel or WES. There is now genomic information available from 208 biopsy samples from 193 patients, being 128 samples sequenced by targeted panel, and 80 by WES. At present, most of this information together with their clinical data is uploaded in cBioPortal with a control access by a password. This security control, implemented with the collaboration of the IT team at VHIO, allows access and visualization only to the user's projects maintaining the data confidentiality. Furthermore, this platform and data are currently stored and protected in VHIO servers.

Further steps: we plan to incorporate a PDX genomic project with the aim to visualize PDX data with clinical data from patients who donor the sample and other relevant information from PDX itself. Besides, there are other local projects from additional research teams under development to be progressively uploaded into the platform.

Aim 3.

According to the methodology previously described, we have designed the preliminary experience evaluation tool after several consecutive steps. First, a literature review was carried out identifying studies related to this topic to analyze the questionnaires developed and the items included. Most were focused on knowledge, not pathology-oriented, and none of them were in Spanish (according to our population). After translating the potentially relevant items, a revision and selection were made first by prostate cancer medical oncologists, and then by a patient advocate. The final item selection covering different topics related to the patient experience around genomic testing and result communication was included in a pre-genomic testing questionnaire and in a different post-genomic testing questionnaire. The pre-genomic testing questionnaire was designed considering demographic questions (n=8 items), knowledge (n=12), and three experience domains (expectations (n=11), concerns (n=4), and attitudes (n=11), using a Likert scale with 5 levels), plus an open question was included with space to describe its expectations. The post-genomic testing questionnaire included a general experience and participation view (n=2 items), and the three experience domains (expectations (n=11), concerns (n=4), and attitudes (n=5), using the same Likert scale with 5 levels), plus a final section was added oriented to the expectations fulfilled (1 multiple option question and an (analog visual scale, AVS).

The local study was started during Q1-Y1, and the last questionnaire was collected by Q2-Y2. A total of 30 patients were recruited and 27 questionnaires pre-, and 25 post-genomic testing were available and included in the analysis. Among demographics, most were married (93%), retired (81.5%), and without a high-level education (primary school 40.7%, and college 18.5%). Regarding knowledge, the mean of the total score was 3.6, sd 2.3 (considering a score range from 0 to 10). There was a total score significant difference between patients with high-level education (mean 5.0, sd 2.2) and those with only primary or college (mean 3.0, sd 2.0) (p-value=0.04). Then, each item was evaluated according to the variability of the responses, the relationship with the total score, and its relevance. Thus, five items were selected. Then, the expectations, concerns, and attitudes domain were analyzed. After the different sequential analytical steps, 14 items were selected and grouped by the EFA plus 3 additional items (not included in the EFA) due to the relevant meaning. The same list of items was retained in the post-genomic testing questionnaire.

Regarding the ongoing SOLTI-2102-HOPE-Prostate study and the experience evaluation tool analysis, by the database look in December, 50 patients were recruited with pre-genomic testing questionnaires. Since the HOPE-Prostate study was launched before the end of the pilot study at VHIO, the same preliminary experience evaluation tool was used. Besides, we considered that the larger sample size and the type of population (national) in the HOPE-Prostate study could improve the design and item selection. Out of these 50, 88% were married, 54% were retired, and 50% did not have a high-level education (high-level 44%, unknown 6%). Regarding knowledge, the mean of the total score was 2.0, sd 1.0. There was no significant difference between patients with high-level education (mean 2.2, sd 1.2) and primary or college (mean 1.9, sd 0.9) (p-value=0.5). Then, the same approach applied in the local pilot study at VHIO was pursued to identify the most relevant and useful items in this cohort. While the same 14 items were finally selected, how they were grouped by the EFA in this cohort was not equal to the prior analysis. However, in this cohort results were more robust and consistent, considering the grouping by the EFA more reliable; besides, the sample size in the local pilot study was considerably smaller. The final items were: expectations (1- The result will help control my cancer; 2- The result will help to increase my life expectancy; 3- My Dr will explain to me the results and their implications for my health; 4- I will have additional therapeutic options; 5- I will reach experimental treatments), concerns (1- I am concerned that the results could not guide my treatment; 2- I am concerned that the results could be difficult to understand; 3- I am concerned that the results could provide information that I would prefer not to know; 4- The results could concern me or produce anxiety; 5- Genomic testing seems to be an inaccurate test; 6- I have received enough information to understand the risks and benefits of the genomic testing), and attitudes (1- I am willing to have a minor procedure (biopsy) to obtain another sample for genomic testing; 2- I am willing to have a major procedure (surgery) to obtain another sample for genomic testing). Finally, I explored descriptively the results with these selected items in the HOPE-Prostate cohort. The mean expectations score was 26.18 (sd 3.4) (possible range 0-30), the mean for concerns was 3.2 (sd 5.4) (possible range -10 to 20), and the mean for

attitudes was 7.0 (sd 3.0) (possible range 0-10). Looking for relationships between these domains and sociodemographics as well as knowledge, no differences were observed. The mean percentage of the expectations fulfilled in this cohort, according to the AVS in the post-questionnaire, was 65.7 (ds 34.2).
Please **go to this link** to see the whole analysis and these preliminary results. This eBook is a draft for inner use to show the analysis, share the results easily, and discuss new or different approaches to the analysis. This is an example of how we usually work and how I share my results and analysis.

Regarding the SOLTI-2102-HOPE-Prostate study, I have been actively involved in the protocol and the statistical analysis plan development. The ethics approval was gained in Nov 2022, and the first patient enrolled in March/2023. As the medical fellow of this study, I am leading this project as well as the virtual bi-weekly molecular tumor board where the genomic results are discussed accompanied by the medical record summary of each patient. By December 2023, 105 subjects registered to participate and 91 could be successfully included. In 52 of them, genomic testing could be performed, and 49 cases had been discussed by the molecular tumor board with the subsequent report delivered. We sent an abstract as a Trial in Progress to the ASCO 2024 meeting [Abstract Ref 2].

Further steps: while we continue with the SOLTI-2102-HOPE-Prostate study and the sub-study about patients' expectations, a new analysis is planned by the end of February having a target sample size of 80 patients, to refine and complete the EFA and the development of the experience evaluation tool. An abstract with these results will be sent to ESMO Congress 2024. Posteriorly, an additional Confirmatory Factor Analysis will be pursued. Then, with the definitive experience evaluation tool the descriptive results and analysis will be presented for the following whole cohort.

Other Projects
At the beginning of the Fellowship and considering the importance of genomics in prostate cancer and the clinical impact of DNA repair gene alterations on prognosis, treatment selection, and its response; under the supervision of Dr. Mateo, I have written a review article. This paper explains and discusses the clinical implications of homologous recombination repair (HRR) mutations in prostate cancer, including theoretical aspects of DNA repair mechanisms, the genomic landscape of prostate cancer, the role of HRR mutations in different stages of the disease, and practical considerations regarding how to evaluate these alterations in clinical practice. The article was part of a special issue in prostate cancer genomics in The Prostate Journal [See below, Ref 2].

In line with the understanding of prostate cancer genomics, during Q2-Y1, I joined the project entitled “Prostate Cancer genomic evolution and signatures of DNA damage repair deficiencies”, from the Prostate Cancer Translational Research Group. In this project, I have been involved in data analysis and interpretation. I have been developing machine learning models with genomic scars to predict an HRD status. Novel strategies were applied to identify the most relevant altered genes linked with each scar. Then, I was focused on the comprehensive study of one of these scars (LST), to understand and identify the key elements that determined its development in prostate cancer. *Further steps:* This project is currently ongoing and I will continue collaborating and exploring the relationship between genomic signatures and treatments. It is planned to expand the dataset as well as to incorporate RNAseq data.

As part of the Oncology Data Science (ODysSey) Group, I worked on a project to study the role of surrogate endpoints in the population of patients receiving immune checkpoint inhibitors. This project aimed to determine the correlation of different surrogate endpoints with overall survival. Data from clinical trials were extracted after a systematic review and different outcomes were analyzed regarding overall survival. I have been involved in the systematic review, data collection, data analysis, and manuscript preparation [See below, Ref 3].

Linked with my role in the ODysSey Group and my work with real-world data, and with the aim of expanding my oncology network; at the beginning of Y2, I joined a collaborative research group of oncologists from several

countries across Europe led by Dr. Pellat (Hôpital Cochin, Paris) and Dr. Grinda (Gustave Roussy, Paris) and in collaboration with ESMO Real-World Data and Digital Health Working Group, to participate in a project of Real Word Evidence (RWE) in oncology. Considering RWE in oncology is a field of growing interest with an increasing number of publications over time but with a great heterogeneity between studies (such as the clinical setting, methodology used, or reporting); there is a need to understand and map this evidence to improve how future research will be done. Thus, a project was designed based on a systematic review aimed at analyzing RWE studies focused on targeted therapies in clinical oncology published during 2020-2022. The PubMed search was carried out, the full extraction of all the articles was completed, and the analysis was performed. The first part of the project has been presented in ESMO as a Proffered Paper under the title "Comprehensive mapping review of real-world evidence publications focusing on targeted therapies in solid tumors: A collaborative work from ESMO real-world data and Digital Health Working Group" [See other presentations, Abstract Ref 3]. Now we are finishing the manuscript which is expected to be submitted to ESMO Open by the end of February.
In this project, I participated in article extraction, carried out the statistical analysis, developed the figures for both the ESMO presentation and the manuscript, and participated in the manuscript elaboration.

Last year, working in the Prostate Cancer Translational Research Group, I collaborated on a study analyzing the role of extracellular vesicles in metastatic prostate cancer. The first results were presented as an abstract at the AACR annual meeting 2023, Orlando, Florida [See other presentations, Abstract Ref 4]. Moreover, the final results of this project have been incorporated into a manuscript that is currently in the second review round in a high-impact Journal.

Finally, as part of further collaborations inside VHIO, particularly with the Radiomics Group, I participated in a review already accepted [See below, Ref 4].

During these two years, I have been involved with the Genitourinary Group at the Vall d`Hebron University Hospital. I went weekly to the clinic under supervision to participate in daily clinical assistance to patients. I participated in the Comites and clinical trials meetings as well as other activities organized inside the Group. Besides, I have been also participating in the central Molecular Tumor Boards at VHIO led by Dr Dienstmann, and I presented a case in the past December.

List of Publications and Presentations Resulting from the Translational Research Project "Integration of genomic testing and patient expectations into prostate cancer treatment decision-making"

[1] Sara Arce-Gallego*, Pablo Cresta Morgado*, Luisa Delgado-Serrano*, Sara Simonetti*, Macarena Gonzalez, David Marmolejo, Rafael Morales-Barrera, Gisela Mir, Maria Eugenia Semidey, Paula Romero Lozano, Sarai Cordoba-Terreros, Richard Mast, Matias de Albert, Jacques Planas, Mercè Cuadras, Xavier Maldonado, Cristina Suarez, Irene Casanova-Salas, Lara Nonell, Rodrigo Dienstmann, Paolo Nuciforo, Ana Vivancos, Alba Llop-Guevara, Joan Carles, Violeta Serra, Joaquin Mateo. Evaluation of homologous recombination repair status in metastatic prostate cancer by next-generation sequencing and functional tissue-based immunofluorescence assays. bioRxiv 2024.01.28.577367; doi: https://doi.org/10.1101/2024.01.28.577367

[2] Cresta Morgado P, Mateo J. Clinical implications of homologous recombination repair mutations in prostate cancer. Prostate. 2022 Aug;82 Suppl 1:S45-S59.
Available as open access here: https://doi.org/10.1002/pros.24352.

[3] Villacampa G*, Cresta Morgado P*, Navarro V, Viaplana C, Dienstmann R. Comprehensive evaluation of surrogate endpoints to predict overall survival in trials with PD1/PD-L1 immune checkpoint inhibitors plus chemotherapy. Cancer Treat Rev. 2023;116:102542. doi:10.1016/j.ctrv.2023.102542

Congress presentations

- ➔ [Abstract Ref 1]. Pablo, Cresta Morgado; Sara, Arce-Gallego; Luisa, Delgado-Serrano; Sara, Simonetti; Macarena, Gonzalez; David, Marmolejo; Rafael, Morales Barrera; Jacques, Planas; Paula, Romero-Lozano; Xavier, Maldonado; Cristina, Suarez; Mariona, Figols; Sara, Cros; Rodrigo, Dienstmann; Paolo, Nuciforo; Ana, Vivancos; Alba, Llop-Guevara; Joan, Carles; Violeta, Serra; Joaquin, Mateo. Evaluation of homologous recombination repair (HRR) status in metastatic prostate cancer by next-generation sequencing and functional tissue-based immunofluorescence assays. 2024 ASCO Annual Meeting. **Under review.**
- ➔ [Abstract Ref 2]. Pablo Cresta Morgado; Tomás Pascual; Rubén Olivera-Salguero; Iria Martínez; Fernando Salvador; Ángel Borque-Fernando; Antonio Rosino; María José Donate; Antonio Gómez-Caamaño; Almudena Zapatero; Fernando López-Campos; Elena Castro; Judith Balmaña; Arkaitz Carracedo; Enrique Gallardo; Verónica Calderero; Ana Vivancos; Juan Manuel Ferrero-Cafiero; Joaquin Mateo; Joan Carles. SOLTI-2102 HOPE Prostate: Real world clinical practice study to assess the feasibility and impact of liquid biopsy-based genomic profiling on treatment decision making for patients with metastatic prostate cancer in Spain. 2024 ASCO Annual Meeting. **Under review.**

List of Publications and Presentations resulting from other projects during the fellowship period (if applicable)

[4] Raquel Perez-Lopez, Marta Ligero Hernandez, Bente Gielen, Victor Navarro, Pablo Cresta, Olivia Prior, Rodgrigo Dienstmann, Paolo Nuciforo, Stefano Treschi, Regina Beets-Tan, Evis Sala, and Elena Garralda. A whirl of radiomics-based biomarkers in cancer immunotherapy, why is large scale validation still lacking?. npj Precision Oncology. Accepted 27/Jan/24.Raquel Perez-Lopez, Marta Ligero Hernandez, Bente Gielen, Victor Navarro, Pablo Cresta, Olivia Prior, Rodgrigo Dienstmann, Paolo Nuciforo, Stefano Treschi, Regina Beets-Tan, Evis Sala, and Elena Garralda. A whirl of radiomics-based biomarkers in cancer immunotherapy, why is large scale validation still lacking?. npj Precision Oncology. Accepted 27/Jan/24.

Congress presentations

- [Abstract Ref 3] Anna Pellat, Thomas Grinda, Arsela Prelaj, Pablo Cresta, Vanjia Miskovic, Antonis Valachis, Ioannis Zerdes, Diogo Martins-Branco, Leonardo Provenzano, Andrea Spagnoletti, Guilherme Nader-Marta, Brooke Wilson, Filippo Montemurro, Luis Castelo-Branco, George Pentheroudakis, Suzette Delaloge, Miriam Koopman. Comprehensive mapping review of real-world evidence publications focusing on targeted therapies in solid tumors: A collaborative work from ESMO real-world data and Digital Health Working Group. Proffered paper. ESMO Congress 2023.
- [Abstract Ref 4] Irene Casanova-Salas, Sarai Córdoba-Terreros, Daniel Aguilar, Laura Agúndez, Julián Brandariz, Nicolás Herranz, Alexandre Sierra, Pablo Cresta, Maria del Mar Suanes, Mario Soriano, Elena Castellano, Javier Hernández, Héctor Peinado, Joan Carles, Joaquin Mateo. Circulating tumor extracellular vesicles to monitor metastatic prostate cancer genomic and transcriptomic evolution in plasma. AACR annual meeting 2023, Orlando, Florida.

Selection of Courses and Workshops Attended During the Fellowship

As part of my training in prostate cancer, I attended:

- ESMO Preceptorship on Prostate Cancer on October 20-21, celebrated in Lugano, Switzerland.
- "Management of Advanced prostate cancer: multidisciplinary approach" on March 24-25, celebrated at VHIO, Spain.

As part of my training in data science, I pursued:

- Functional analysis of omics data using public tools, on November 24th and 29th, and December 1st, 2022; coordinated by the VHIO Academy.
- REDCap training, on September 29-30, 2022; at VHIO.
- Python workshop: Introduction to Python and Data analysis and visualization, on May 18th and June 15th, 2022; coordinated by the VHIO Academy.
- Exploring public cancer data through web resources, on October 6th, 9th, and 11th, 2023; coordinated by the VHIO Academy.

Acknowledgements

I would like to thank, first and foremost, all the patients because they are in the center of the scene, and without their consent, no project could be carried out; Dr. Mateo and Dr. Dienstmann for their mentorship, and ESMO because without its support nothing could be possible.

Personal Statement (not mandatory)

While my work as a medical and translational research fellow will continue in VHIO working with both teams, the Prostate Cancer Translational Research Group and the Oncology Data Science (ODysSey) Group, most of the aims and objectives were successfully achieved.

During these two years, I could fully integrate both research teams working in an amazing interdisciplinary environment boosting my skills and background with the excellence and experience of both groups and Mentors. Moreover, I could leverage the vast spectrum of opportunities that VHIO offers, from academic training instances to the expansion of my professional network by collaborating with teams such as Radiomics. Besides, the possibilities that this Fellowship and the VHIO environment provided enabled me to expand my network beyond Vall d'Hebron by collaborating with other young ESMO oncologists and the ESMO real-world data and Digital Health Working Group.
I have been working on different objectives and points of my research project as well as I could be involved in other projects belonging to both groups. To highlight the most important and challenging aspects, I have been able to design a set of patient-centered questionnaires around genomic testing and implement them into a clinical research study; besides, through this project and opportunity, I am already fully involved in the national study (SOLTI-2102-HOPE-Prostate). The data collection (extraction, registration, curation, and validation) and patient enrollment have been the hardest and most challenging steps. Furthermore, one of the greatest and also challenging works and analyses was the additional project developed in the Prostate Cancer Translational Research Group aimed to study HRR in prostate cancer, which I am currently co-leading; results from this project are materialized in a manuscript prompt to be submitted. Indeed, through this project, I could expand my knowledge and skills in programming for data science and statistics applied to oncology. I strongly believe that now, I thoroughly understand how to design and execute translational projects in the digital oncology space.

Undoubtedly, the ESMO Research Fellowship - Translational Focus has been an extraordinary learning opportunity that allows me to complete a key professional and training step in the path to becoming a clinician scientist.

References
1. de Bono, J. et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. N. Engl. J. Med. 382, 2091–2102 (2020). 2. Abeshouse, A. et al. The Molecular Taxonomy of Primary Prostate Cancer. Cell 163, 1011–1025 (2015). 3. Mateo, J. et al. Genomics of lethal prostate cancer at diagnosis and castration resistance. J. Clin. Invest. 130, 1743–1751 (2020). 4. Sweeney, C. J. et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. N. Engl. J. Med. 373, 737–746 (2015). 5. James, N. D. et al. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. N. Engl. J. Med. 377, 338–351 (2017). 6. Davis, I. D. et al. Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. N. Engl. J. Med. 381, 121–131 (2019). 7. McFarland, D. C. et al. Communicating About Precision Oncology. JCO Precis. Oncol. 1–9 (2017). 8. Wolyniec, K. et al. Understanding and information needs of cancer patients regarding treatment-focused genomic testing: A systematic review. Psychooncology. 29, 632–638 (2020).

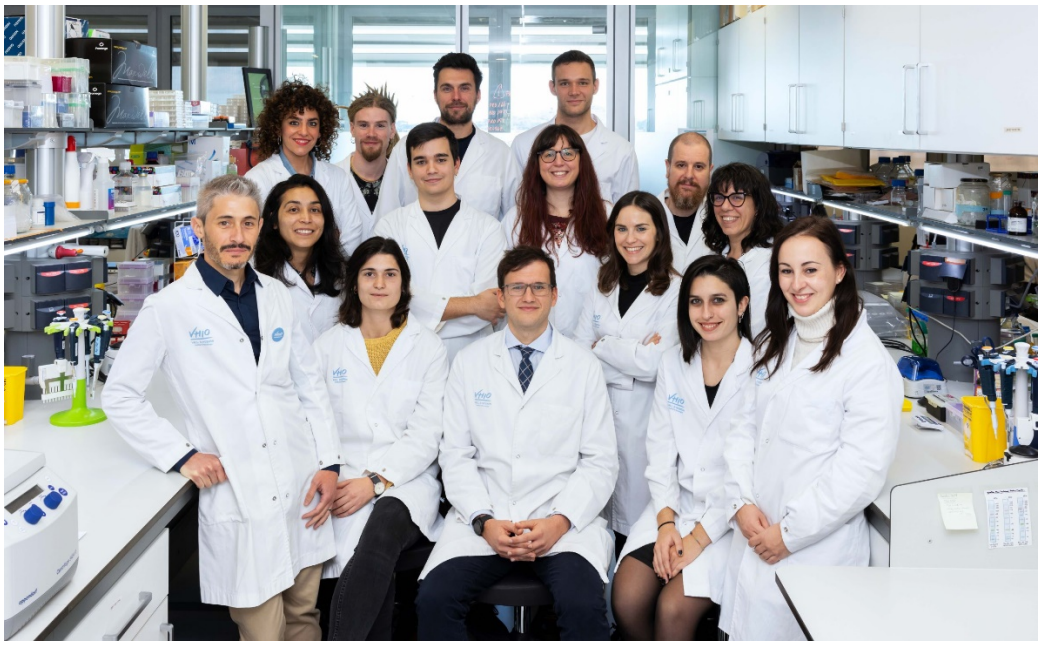
SIGNATURES	
Award Recipient full name	***Signature and Date***
Pablo Damián Cresta Morgado	 8-Feb-2024

Research Mentor full name	***Signature and Date***
Joaquin Mateo	 8-Feb-2024

Research Mentor full name	***Signature and Date***
Rodrigo Dienstmann	 8-Feb-2024

Insert photo of yourself and/or colleagues at the host institute (not mandatory)

Prostate Cancer Translational Research Group



Oncology Data Science (ODysSey) Group

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