ESMO Clinical Research Fellowship

(January 2020 – January 2021)

CARLO CATTRINI

FINAL REPORT

Host Institute: **National Cancer Research Center (CNIO), Madrid, Spain**
Mentor: **David Olmos**
Project title: **BRCA2MEN: an international, multicentre, observational and ambispective study to validate the predictive value of germline BRCA2 mutations in selecting first-line metastatic castration-resistant prostate cancer (mCRPC) treatment.**

Home Institute: **Ospedale Policlinico San Martino – University of Genoa, Genoa, Italy**

Introduction

Alterations in the DNA damage repair (DDR) pathways have recently been recognized as a major hallmark of prostate cancer. Next-generation sequencing (NGS) studies have revealed that about 10% of primary tumours and 25% of metastases from prostate cancer harbour DDR defects (Armenia et al., 2018; Robinson et al., 2015). Importantly, these DDR defects have been identified in the germline of 8-17% of patients with metastatic disease (Castro et al., 2019; Nicolosi et al., 2019; Pritchard et al., 2016). BRCA2 aberrations that impair the gene function are consistently described as the most common DDR event both in the somatic- and germlines (Abida et al., 2017; Castro et al., 2019). Germline BRCA2 mutations have been associated with more aggressive disease and poor clinical outcomes (Castro et al., 2015; Castro et al., 2013), but the prognostic implications of other DDR genes are less well established.

Rationale and Aim

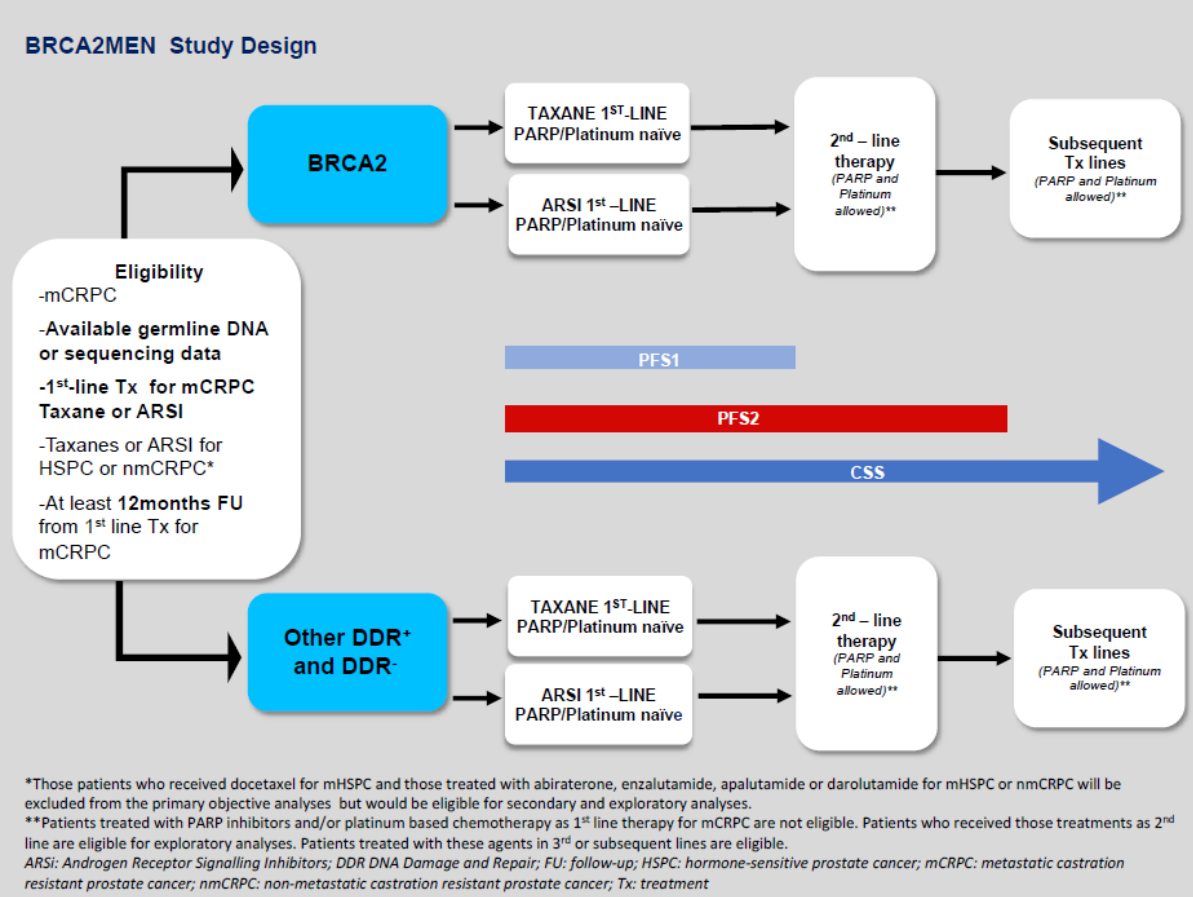
The Team of the Prostate Cancer Clinical Research Unit at CNIO has recently reported the results of the first prospective study that ascertained the impact of germline DDR mutations on outcomes of patients with mCRPC (Castro et al., 2019). The PROREPAIR-B study included 419 unselected mCRPC patients screened for a panel of 107 genes involved in DDR. In the study, germline BRCA2 carriers showed a shorter time to castration-resistance compared to non-carriers (13.2 vs 28 months, respectively, p=0.05). Survival from mCRPC diagnosis was halved in BRCA2 carriers compared to non-carriers (17 vs 33 months, respectively, p=0.027). The difference remained significant when BRCA2 carriers were compared to other germline DDR carriers (median 33.8 months, p=0.048). Multivariate analyses identified BRCA2 as an independent prognostic factor for CSS in mCRPC (HR 2.11, 95%CI 1.06-4.18). Interestingly, the outcomes of BRCA2 carriers who received abiraterone or enzalutamide as first-line treatment did not differ from that of non-carriers. Conversely, BRCA2 carriers treated with first-line taxane showed shorter PFS2 (8.6 vs 17.1 months, respectively, p<0.0001; HR: 8.16 95% CI 3.60-18.49) and had significantly worse CSS (10.7 vs 28.4 months, p=0.0003; HR: 4.16, 95%CI 1.80-9.62) compared to non-carriers who received the same treatment. No biomarker has been identified to date to select one therapy over another in the setting of advanced prostate cancer. If these preliminary results are confirmed, determination of germline BRCA2 status would be of assistance for the selection of the first-line of treatment in mCRPC.

Primary aim and primary endpoint
To validate the predictive value of germline BRCA2 mutations for PFS2 according to first-line abiraterone/enzalutamide versus taxane therapy for mCRPC. Endpoint: difference in PFS2 at 12 months between BRCA2 patients receiving each 1st-line treatment-class.
Secondary aims

1. To analyse the impact of germline BRCA2 status in CSS, progression-free survival (PFS), response rate according to treatment line and/or treatment type.
2. To explore the impact of germline mutations in BRCA1, ATM or any other DDR with a frequency >1% in PFS2, CSS, PFS, response rate according to treatment line and/or treatment type.
3. To explore the effect on CSS of poly ADP-ribose polymerase inhibitors (PARPi), platin salts, other alkylating agents and synthetic lethality strategies.
4. To estimate the prevalence of germline DDR mutations across different countries and potential clinic-pathological associations in order to inform the most appropriate screening strategies.

Experimental design

This study is defined as an international, multicentre, observational and ambispective study. The project aims at building a multi-institutional international series of approximately 1000 patients enrolled in prospective and/or retrospective studies in which germline DNA is available for analyses (or germline BRCA2 status has been screened). Patients in this pooled cohort will proceed from prospective cohorts that have completed enrolment and have long-term follow-up available, or regional/local series or registries approved under local protocols. It will be performed targeted-exome sequencing for a panel of 53 DDR genes in patients when there is not mutational status available or re-analyse whole-exome sequencing (WES) or whole-genome sequencing (WGS) germline data when previously available according to our analysis's pipelines. Data will be also collected from mCRPC patients in which germline BRCA2 status is available and who have not received an alkylating agent and/or PARPi for prostate cancer or they have received them after at least 2 standard treatment lines for mCRPC. Then germline DNA samples (or available sequencing data), tumor features, baseline data and clinical outcomes will be collected. If possible, a predictive tool based on the family history of cancer of participating men will be also developed to optimize germline screening.



Results, Conclusions and Future Perspectives

I have been working on the BRCA2men project since January 2020. After several meetings with my mentors and with other colleagues to revise protocol drafts, the protocol of BRCA2men study (v1.0) and the feasibility questionnaire were completed and sent to potential participating centres.
A preliminary collection and revision of patients' data from some Spanish centres was started. Overall, about 400 patients from 42 Spanish hospitals were identified as potential candidates to be included in the BRCA2men study. The majority of these patients had already signed the informed consent, given that the PROCURE platform, which includes the PROSABI, PROSENZA and PRORADIUM studies, allowed the enrolment of patients in the BRCA2men project. Some centres were monitored to solve queries on data about first and second treatment lines of patients with metastatic castration-resistant prostate cancer. Several other centres in Europe and in the rest of the world have been contacted (Australia, Belgium, Canada, France, Germany, Holland, Hong Kong, Iceland, Ireland, Israel, Italy, New Zeland, Poland, Portugal, Singapore, Sweden, Switzerland, Turkey, United Kingdom and USA). Centres in Italy, Portugal, Turkey, Holland, Singapore, Australia and United Kingdom signed the feasibility questionnaires.
We also started with the analysis of 400 Spanish patients and additional 300 patients from the Italian MEET-URO group.

However, the coronavirus pandemic has significantly impacted on scientific research and European collaborations. From march 2020, Spain and Italy reported a relevant number of cases and limitations have been applied to the research centres, such as CNIO. Despite the revision of data from Spanish centres has been continued, the centres in Spain and Europe were largely unable to provide data and to allow monitoring. Therefore, the BRCA2men project has currently not concluded.
The abstract "BRCA2men: an international, multicentre, observational and ambispective study to validate the predictive value of germline BRCA2 mutations for selecting the first-line of treatment in metastatic castration-resistant prostate cancer (mCRPC)" was accepted to ESMO Congress 2020 as a poster of trial in progress.
During this particular moment, I have carried on and collaborated to other projects (see publications below). These works have offered the opportunity to reinforce the collaboration between CNIO and the University of Genova.

Given my personal inability to continue to work in Madrid during 2021, I decided to return to Italy and I accepted a position as medical oncologist at the genitourinary section of the "Maggiore della Carità" University Hospital in Novara. Thanks to the presence of several preclinical laboratories and academic units within the University of Eastern Piedmont (Novara), this position allows me to continue my career as physician-scientist and academic researcher in Italy. In addition, I'm going to continue the 3-year PhD Programme started in 2019 at the University of Genoa, focused on the BRCA2men project. My plan is to continue to collaborate with the Prostate Cancer Team in Madrid to complete this project and to start new international research projects in the field of genitourinary malignancies.

List of Publications and Presentations Resulting from the Translational Research Project "BRCA2MEN: an international, multicentre, observational and ambispective study to validate the predictive value of germline BRCA2 mutations in selecting first-line metastatic castration-resistant prostate cancer (mCRPC) treatment"

- 692TiP BRCA2men: An international, multicentre, observational and ambispective study to validate the predictive value of germline BRCA2 mutations for selecting the first-line of treatment in metastatic castration-resistant prostate cancer (mCRPC). Cattrini C., Lozano R., Conteduca C., Ruizo-Vico M., Lolkema M., Lorente D., Sandhu S., Romero N., Loriot Y, Azad A.A., Costa L., Vincenuex A., Kanesvaran R., Urun Y, Puente J, Attard G, Mehra N., De Giorgi U., Olmos D., Castro E. Annals of Oncology, Volume 31, S547 - S548 (2020).
- Genetic aberrations in DNA Repair pathways: a cornerstone of precision oncology in Prostate Cancer. Lozano R, Castro E, Aragon I, Cendon Y, Cattrini C, Lopez-Casas P, Olmos D. British Journal of Oncology, 124, pages 552–563 (2021).
- BRCA mutations in prostate cancer: prognostic and predictive implications. Messina C, Cattrini C, Soldato D, Vallome G, Caffo O, Castro E, Olmos D, Boccardo F, Zanardi E. Journal of Oncology, vol. 2020, Article ID 4986365, 7 pages, 2020.

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

cnio stop cancer

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

- Barranco R, Messina C, Bonsignore A, Cattrini C, Ventura F. Medical Liability in Cancer Care During COVID-19 Pandemic: Heroes or Guilty? Front Public Health. 2020 Dec 18; 8:602988.
- Messina C, Salati M, Messina M, Cattrini C, Merz V, Caffo O. Efficacy and safety of PD1/PDL1 blockade with platinum-based chemotherapy for extensive small cell lung cancer: A pooled analysis of randomized trials. Eur J Clin Invest. 2020 Dec 31:e13483.
- Pedrazzoli P, Rondonotti D, Cattrini C, Secondino S, et al. Metastatic Mediastinal Germ-Cell Tumor and Concurrent COVID-19: When Chemotherapy Is Not Deferrable. Oncologist. 2020 Dec 20. doi: 10.1002/onco.13647.
- Cerbone L, Cattrini C, Vallome G, Latocca MM, Boccardo F, Zanardi E. Combination therapy in metastatic renal cell carcinoma: Back to the future? Semin Oncol. 2020 Dec;47(6):361-366.
- Cattrini C, Capaia M, Boccardo F, Barboro P. Etoposide and topoisomerase II inhibition for aggressive prostate cancer: data from a translational study. Cancer Treat Res Commun. 2020; 25:100221.
- Cattrini C, Soldato D, Rubagotti A, Zinoli L, Zanardi E, Barboro P, Messina C, Castro E, Olmos D, Boccardo F. Epidemiological Characteristics and Survival in Patients with De Novo Metastatic Prostate Cancer. Cancers (Basel). 2020 Oct 3;12(10): E2855.
- Cattrini C, Bersanelli M, Latocca MM, Conte B, Vallome G, Boccardo F. Sex Hormones and Hormone Therapy during COVID-19 Pandemic: Implications for Patients with Cancer. Cancers (Basel). 2020 Aug 18;12(8):2325.
- Cattrini C, Barboro P, Rubagotti A, Zinoli L, Zanardi E, Capaia M, Boccardo F. Integrative Analysis of Periostin in Primary and Advanced Prostate Cancer. Transl Oncol. 2020 Jul;13(7):100789.
- Lorente D, Castro E, Lozano R, Puente J, Romero-Laorden N, Rodríguez-Vida A, Lainez N, Villatoro R, Llácer C, Cattrini C, et al. PROREPAIR-B Study Investigators. Association Between Second Progression-free Survival (PFS2) and Overall Survival in Metastatic Castration-resistant Prostate Cancer. Eur Urol. 2020 Jun;77(6):763-766.
- Messina C, Messina M, Cattrini C. From astrology to prostate cancer: what is the role of subgroup analyses? Ann Oncol. 2020 Mar;31(3):437-438.

Selection of Courses and Workshops Attended During the Fellowship

- 2020 ASCO Genitourinary Cancers Symposium in San Francisco. Winner of the 2020 Conquer Cancer Foundation of ASCO Merit Award with the Poster entitled “Real-world survival improvements in patients with newly diagnosed metastatic prostate cancer treated in the United States”.
- ESMO Virtual Congress 2020

Acknowledgements

I thank my mentors, Dr. David Olmos and Dr. Elena Castro, who were always ready to answer to my questions and supported my personal and professional growth, improving my knowledge in the field of DNA repair defects and prostate cancer. I thank ESMO that offered me the opportunity to build my career as physician-scientist in an international centre of excellence.

Personal Statement

During my staying at CNIO, I have learned common mistakes and challenges to face during the design of a clinical study. I attended the weekly meetings of the Prostate Team, in which we discussed problematics and new updates in prostate cancer discoveries. In the lab, I have learned how to manage and process blood samples for germline DNA analysis and understood the limits of next-generation sequencing. I have also socialized with the Prostate Team and with other colleagues, improving my knowledge in translational research and in biostatistics. Despite the coronavirus outbreak has significantly impacted on the progress of my project, the BRCA2men study allowed me to know and to meet international experts of prostate cancer research around Europe and the World, paving the way for future profitable collaborations. Overall, I improved my knowledge in basic and clinical research, I feel very satisfied with my experience and grateful to ESMO for this opportunity.

References

SIGNATURES	
Award Recipient full name	***Signature and Date***
CARLO CATTRINI	15-March-2021

Research Mentor full name	***Signature and Date***
DAVID OLMOS	3-Mar-2021

This ESMO Clinical Fellowship Research Project was supported by an educational grant from ESMO.