PROSTATE CANCER JUNIOR CLINICAL RESEARCH UNIT

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OVERVIEW

Prostate cancer (PrCa) is the most common cancer and the 2nd leading cause of cancer mortality among men in Western countries. Despite advances in diagnosis and early-disease treatment, up to 30% of PrCa patients will develop metastasis at some point and succumb after the acquisition of a castration-resistant status (mCRPrCa). The early identification of PrCa patients with greater predisposition to develop aggressive mCRPC could lead to the development of novel treatment strategies and improved outcomes. In addition to AR aberrations following androgen-deprivation therapy leading to resistance to current treatment options, DNA repair defects have been identified in about 5% and 25% of early PrCa and mCRPC, respectively. Seminal work from our Group, and others, has established that some alterations, e.g. germline *BRCA1/BRCA2* deleterious mutations, are linked to poor outcomes. Currently, we lack the adequate biological knowledge and reliable biomarkers to select the right treatment for the right patient at the right time.

RESEARCH HIGHLIGHTS

PROCURE biomarkers platform

This network was started by our Group in 2013; it currently has 5 ongoing prospective studies (PROREPAIR, PROSTAC, PROSABI, PROSENZA, PRORADIUM) in mCRPC in 63 participating centres with over 900 enrolled patients.

PROREPAIR study

This is a prospective multicentre cohort study involving 50 Spanish centres within the PROCURE network. By April 2016, 432 mCRPC patients were enrolled to evaluate the prevalence and impact of DNA repair germline mutations in mCRPC survival and the response to systemic treatments for mCRPC. Germline mutations were analysed in the following genes: *ATM, ATR, BARD1, BRCA2, BRCA1, BRIP1, CHEK2, GEN1, MLH1, MRE11A, MSH2, MSH6, NBN, PALB2, PMS2, RAD51C, RAD51D and XRCC2*. Current results suggest that up to 12% of the patients in this series harbour a germline deleterious mutation. Analyses of the clinical impact of germline and somatic mutations in outcomes are still undergoing. BRCARAD and BRCAPROS studies, although in a retrospective fashion, will address similar questions at an early prostate cancer stage.

SWITCH Phase II study

In 2016, we also completed the enrolment and follow-up of our first clinical trial, 'Phase II pilot study of the prednisone to dexamethasone switch in mCRPC patients with progression on abiraterone and prednisone', aimed at analysing the role of certain steroids in the resistance and response to novel androgen-synthesis inhibitors in 26 patients. A simple change in prednisone to dexamethasone rescued the sensitivity to abiraterone and prolonged the time benefiting from this treatment in 40% of the patients; such responses could be linked to AR mutations detected in ctDNA.

Biological characterisation of *BRCA2* and *ATM* mutated tumours

Initial results from human tumour characterisation and mouse models conducted by our Group support that BRCA2 germline and/or somatic alterations may occur early in cancer progression, and that ATM aberrations will favour cancer progression and early intratumour heterogeneity. ■

Graduate Students
Ylenia Cendón, Lorena Magraner (since April), Paz Nombela, Floortje Van De Poll (until May)

Technician
Vanessa Cañadilla

Student in practice
Noemi Hernández (since September)

Visiting scientists
Teresa Garcés (since February), Gala Grau (since June), Ana M. Gutiérrez (since May), Fernando López, Maria I. Pacheco, Leticia Rivera (since May)

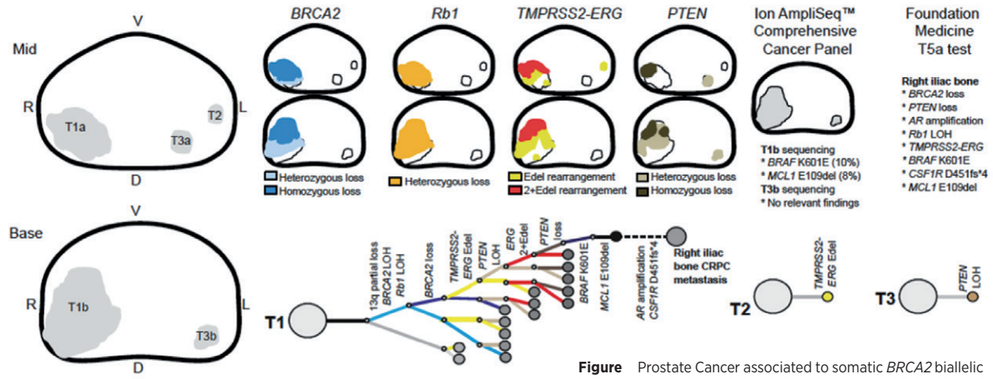

Figure Prostate Cancer associated to somatic *BRCA2* biallelic loss. Heterogeneity and clonal diversity was established based on the frequency and distribution of different dominant events for Prostate Cancer by FISH, as well as targeted sequencing focused on primary prostate cancer and a CRPC bone metastasis.

PUBLICATIONS

- Lorente D *et al.* (incl. Olmos D) (2016). Decline in Circulating Tumor Cell Count and Treatment Outcome in Advanced Prostate Cancer. *Eur Urol* 70, 985-992.
- Mateo J *et al.* (incl.Castro E, Olmos D) (2016). DNA Repair in Prostate Cancer: Biology and Clinical Implications. *Eur Urol*. PMID: 27590317.
- Missiaglia E *et al.* (incl. Olmos D) (2016). MicroRNA and gene co-expression networks characterize biological and clinical behavior of rhabdomyosarcomas. *Cancer Lett*. PMID: 27984116.
- Castro E *et al.* (2016). The PROFILE Feasibility Study: Targeted Screening of Men With a Family History of Prostate Cancer. *Oncologist* 21, 716-722.
- Mateo J *et al.* (incl. Olmos D) (2016). A first in man, dose-finding study of the mTORC1/mTORC2 inhibitor OSI-027 in patients with advanced solid malignancies. *Br J Cancer* 114, 889-896.
- Castro E *et al.* (incl. Olmos D) (2016). The Role of PARP Inhibition in the Treatment of Castration-Resistant Prostate Cancer. *Cancer J* 22, 353-356.
- Selfe J *et al.* (incl. Olmos D) (2016). Impact of fusion gene status versus histology on risk-stratification for rhabdomyosarcoma: Retrospective analyses of patients on UK trials. *Pediatr Blood Cancer*. PMID: 28035744.

AWARDS AND RECOGNITION

- Research contract from the *Ramón y Cajal* Programme, *Ministerio de Economía, Industria y Competitividad* (*MEIC*).
- Scientific Committee Member, ESMO Congress, Copenhagen, Denmark.
- Faculty Board Member, EORTC-ECCO-AACR-ESMO Methods in Clinical Cancer Research Workshop, Zeist, Netherlands.
- Nuria Romero was awarded the 'Best Communication' Award, 2nd Androgen Project Meeting in Prostate Cancer, Spain.
- Elena Castro was the recipient of the Best ESMO Fellowship Project (ESMO Congress, Denmark) and the *Juan de la Cierva* Research Contract (*MEIC*, Spain).