GERMLINE DNA REPAIR DEFECTS IN A PROSPECTIVE MULTICENTER COHORT OF METASTATIC CRPC PATIENTS: A INTERIM ANALYSIS OF THE PROREPAIR STUDY

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Background: Prevalence of deletereous germline *BRCA* mutations (gBRCA) in Prostate Cancer (PrCa) is around 2%. Next generation sequencing studies have recently identified more germline mutations in other DNA repair genes (gMUT) with an estimated prevalence of 4.6%. Such mutations are associated to chromosomal instability, which is considered a milestone in cancer progression. Others and we have described that g*BRCA* are associated to more aggressive presentation and worse PrCa outcomes at diagnosis compared with non-carriers. In addition, we described that these gBRCA were also associated with worse metastasis free survival and shorter time to Castration-Resistance PrCa (CRPC) (*Castro, JCO 2013 & Eur Urol 2015*). Further studies are needed to understand the impact of gMUT in PrCa.

Methods: The PROREPAIR study, is a multicentre study with 2-Parts involving 60 Spanish centres within the PROCURE biomarkers-network. Part A consisted in an ambispective collection of PrCa tissue samples for molecular analyses, still undergoing. Here we report on part B that consisted in a Prospective Cohort of mCRPC patients. The aims were to evaluate the frequency and impact of DNA repair gMUT in CSS from mCRPC and the response to standard survival-prolonging approved systemic treatments for mCRPC. Patients of any age with histologycally-confirmed PrCa, mCRPC according to PCWG2/EAU definitions, and who were going or have started within <6 months a first-line treatment for mCRPC were eligible for this study. Patients were prospectively followed-up for response, progression and survival. A 5-mL blood sample was drawn after consent shipped frozen to central-lab for germline-DNA extraction. After DNA quantification and quality control, sequencing libraries to study 173 genes were captured using a Roche-Nimbelgen custom-designed targeted-sequencing panel and ran using an Illumina NextSeq500. After bioinformatics-analysis and study-board discussion, relevant gMUT were validated by capillary-sequencing, aCGH or ddPCR as required. Study statistical design required the observation of 171 deaths among 408 mCRPC patients to demonstrate a HR for CSS since mCRPC diagnosis of 2.0 (estimated median 30months) for at least 5% of *BRCA1/2* gMUT carriers compared to 95% of non-carriers, with and alpha/beta-values of 0.05/0.20 and after a enrolment+follow-up period of 38 months.

Results: Since January 2013 until April 2016, 425 patients were enrolled in the PROREPAIR (Part B) study. Preliminary Analyses are undergoing in 288 patients who have died or have at

least 24 months of follow-up since mCRPC (cut-off July 2016), in which gMUT carrier or non-carrier status have been confirmed by a second method after NGS.

Conclusions: This is the first prospective study aiming to determine the prevalence of DNA-repair gMUT in unselected mCRPC and their impact in PrCa outcomes. Preliminary data will be presented at the meeting. Final analyses are planned after reaching 171 PrCa deaths and are estimated for the end of 2016.

Conflict of Interest Statement: DO have received research funding from Astra-Zeneca, Bayer and Janssen. DO, EC, JMP, JP and EC have received speaker or advisor-fees from Janssen, Astellas, Sanofi and Bayer. DO have acted as advisor for Astra-Zeneca, Roche/Genetech.

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