5082 **Poster Session**

Landscape and impact of germline pathogenic variants (PVs) in metastatic hormone sensitive prostate cancer (mHSPC): Ancillary study of E3805 CHAARTED.

Anis Hamid, Tyler M Chinsky, Matias Vergara, Emily Grist, Gerhardt Attard, Eliezer Mendel Van Allen, Saud Aldubayan, Christopher Sweeney; University of Melbourne, Parkville, Australia; Dana-Farber Cancer Institute, Boston, MA; University College London, London, United Kingdom; South Australian Immunogenomics Cancer Institute, University of Adelaide, Adelaide, Australia

Background: Enrichment of germline PVs in metastatic castration resistant prostate cancer (mCRPC), compared to localized disease, has directly informed genetic testing guidelines. The prevalence and prognostic/predictive associations of such variants are not well characterized in the mHSPC state, in particular the effect of susceptibility mutations related to DNA damage and repair (DDR) pathways. **Methods:** We performed whole exome sequencing of germline DNA derived from whole blood available from patients (pts) in the phase III CHAARTED trial (NCT00309985) of androgen deprivation therapy (ADT) versus ADT plus docetaxel (ADT+D). After filtering for low coverage, variant annotation and effect prediction, PVs from a curated list of 588 prostate cancer-associated genes were reviewed. The prognostic effect of PVs was evaluated within each treatment arm. Endpoints of time to CRPC (ttCRPC), time to clinical progression (ttClinPD), and overall survival (OS) were estimated by Kaplan-Meier method. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were estimated by Cox models evaluating association of endpoints with biomarkers/arm. Multivariable analysis adjusted for metastatic timing and volume. **Results:** Of 137 pts, 135 had unique germline exomes that passed downstream analysis. Most pts had synchronous (66.7%) and high-volume (62.2%) disease. This biomarker cohort showed benefit of adding docetaxel to ADT (ttCRPC: HR 0.55, 95% CI 0.37-0.82; OS: HR 0.68, 95% CI 0.44-1.07). In total, 61 PVs were detected; 49 pts (36.3%) harbored at least 1 PV in 41 different genes. The most frequently-mutated gene was *BRCA2* (6.67%). In addition, PVs were found in DDR-associated genes including *PALB2* (1.48%), *CHEK2* (1.48%), *BRCA1* (0.74%) and *PMS2* (0.74%) for an overall prevalence of 11.1% (15/135). Pts with *BRCA2* PV on ADT alone had shorter ttCRPC compared with men without the PV (UVA: HR 2.67, 95% CI 0.93-7.63, log rank p=0.057; MVA: HR 2.59, 95% CI 0.91-7.39, p=0.074). There was no evidence of a difference in the ADT+D arm (UVA: HR 1.00, 95% CI 0.31-3.25, log rank p=0.1). Supportive data was observed for ttClinPD in ADT arm (HR 2.85, 95% CI 1.01-8.08, log rank p=0.04). Metastatic volume and timing were not significantly associated with germline *BRCA1/2* or DDR PVs. **Conclusions:** The prevalence of germline *BRCA1/2* and DDR PVs in mHSPC is similar to mCRPC and *BRCA2* PV may confer worse outcomes on ADT alone. This supports the need for genetic testing at diagnosis of mHSPC. Research Sponsor: U.S. National Institutes of Health.

Median survival (mos, 95% CI) by arm and *BRCA2* status.

	ttCRPC	ttClinPD	OS
ADT: BRCA2-wt	10.3 (6.18-18.92)	14.9 (11.56-22.01)	42.5 (29.04-52.8)
ADT: BRCA2-mt	4.5 (1.84-NA)	4.5 (1.84-NA)	30.5 (22.64-NA)
ADT+D: BRCA2-wt	19.8 (14.95-29.4)	29.8 (23.62-41.92)	52.1 (43.99-69.62)
ADT+D: BRCA2-mt	23.1 (8.87-NA)	29.4 (14.62-NA)	37.0 (29.44-NA)

wt: wild-type; mt: mutated.