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Investigating Homologous Recombination Deficiency in mCRPC through ctDNA

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Background Homologous Recombination Deficiency (HRD) refers to the impairment of accurate repair of double-strand breaks. This condition can be targeted with poly ADP ribose polymerase inhibitors (PARPi), through synthetic lethality. We investigate this condition in the context of metastatic castration-resistant prostate cancer (mCRPC), using circulating tumour DNA (ctDNA) as a tumour surrogate.

Methods/Results We analysed 366 plasma samples from mCRPC patients. To estimate the tumour fraction in plasma, we used aneuploidy screening (mFAST-SeqS, ichorCNA). Patients with elevated tumour fractions (>5%) were selected for further analysis (147 samples, 131 patients). A gene panel including genes involved in the HR repair pathway as well as other tumour suppressor genes (TSG) associated with an aggressive phenotype (PTEN, RB1, TP53) was designed and revealed a sensitivity 0.5%VAF, when tested with synthetic oligonucleotides. Longitudinal urine samples (n = 9) were available from 2 patients. After removing artefacts and germline variants, mutations in HR genes were identified in 66 patients (49.6%), with 26 (19.5%) patients carrying pathogenic or likely pathogenic mutations. The most frequently altered genes were BRCA2 (14.5%), ATM (13.0%), BRCA1 (9.3%) and CHEK2 (8.33%). At least one TSG was altered in 58 patients (43.6%) and in 42 (31.5%) patients no alterations was detected in cfDNA. The urine samples were concordant with the plasma samples, but exhibited a lower VAF. Next, the concordance of the identified variants in tissue will be assessed.

Conclusion Our data indicate that the presence of tumour-derived nucleic acids in plasma and urine can provide information about the HRD status of the tumour in mCRPC patients. The mutation rates in HR genes and other TSG align with publicly available data from tissue. Therefore, ctDNA and ucfDNA possibly hold promise in the clinical management of prostate cancer, in the context of HRD and PARPi treatments.