Genomics of prostate primary tumor biopsies identify aberrations associating with aggressive disease and those emerging during treatment.

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Background
Actionable oncogenic aberrations in *TP53*, *RB1*, *AR*, *PTEN* and DNA damage repair (DDR) genes are more commonly identified in late-stage metastatic prostate cancer than in primary, locoregional, tumors. These differences, either result of temporal evolution or due to enrichment for poor prognosis genotypic markers in lethal forms of prostate cancer, can be clinically relevant in the context of molecular stratification of prostate cancer for precision medicine strategies.

Methods
We profiled 470 treatment-naïve, diagnostic, prostate cancer biopsies from patients with either concomitant de-novo or who later developed metastatic disease who were being screened for the TOPARP-B trial, an academic phase II study of the PARPi Olaparib in mCRPC. A customized amplicon-based targeted sequencing panel was used (Generead DNAseq Mix-n-Match Panel v2; Qiagen). The prevalence of mutations in an *a priori* selected gene list in this cohort was compared with published datasets for localized and metastatic prostate cancer using Fisher´s exact test. Additionally, we interrogated same-patient, matched, biopsies of castration resistant metastases of 61 patients in this cohort to assess temporal tumor evolution.

Results
Recurrent aberrations in genes and pathways related to lethal prostate cancer were identified, the commonest being mutations and homozygous loss of *TP53*, which were detected in 127/470 (27%) cases. Pathogenic mutations and/or homozygous deletions in genes involved in DNA damage repair pathways were identified in 109/470 (23%) primary untreated tumors. The most commonly affected genes where *BRCA2* (7%), *CDK12*% (5%), *ATM* (4%), BRCA1 (1%), FANCA (1%) and PALB2 (1%). Among patients with locoregional disease at diagnosis, *TP53* ($p<0.001$) and *RB1* ($p=0.07$) aberrations were commoner than expected from locally advanced prostate cancer datasets (TCGA, Cell 2015). DDR gene defects were also commoner: *BRCA2* 8% ($p=0.015$); *CDK12* 5% ($p=0.04$); *ATM* 6% (p=n.s.). No significant differences were observed between patients with locoregional disease at diagnosis who later developed metastasis and those with de-novo hormone-naïve metastatic disease.
Differences between same-patient treatment-naïve and post-treatment metastatic castration-resistant biopsies were identified, with mCRPC samples showing more *AR* gains and mutations, loss of *TP53 and/or RB1* and events in the PI3K/AKT pathway genes. Contrarily, DDR genes status was highly concordant between same-patient pairs of samples.

Conclusion
Our data indicate that prostate tumors leading to lethal forms of prostate cancer are genomically distinct to the locally advanced tumor genomic landscape already and that diagnostic biopsies can be utilized years later for DDR stratification, but not for RB1/TP53/AR aberrations. These data are clinically relevant for the ongoing development of PARP inhibitors and other precision medicine treatments in prostate cancer.

Conflicts of Interest: none
Acknowledgements: Joaquin Mateo, Adam Sharp and Raquel Perez-Lopez are supported by PCF Young Investigators Awards. J. Mateo also acknowledges funding support from LaCaixa Foundation, FERO, Movember Foundation, the US Department of Defense (CDMRP), Sociedad Española de Oncologia Medica (SEOM) and the Spanish Ministry of Science (Instituto de Salud Carlos III)