Abstract# 5063

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ATM and BRCA2 mutations in Metastatic Prostate Cancer Are Associated with Differential Genomic Alteration Profiles from Homologous Recombination Deficient and Proficient Tumors.

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CARIS POA PRECISION ONCOLOGY ALLIANCE

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Comprehensive Cancer Center designated by the National Cancer Institute

Introduction

- PARP inhibitors (PARPi) are approved for patients with metastatic prostate cancer (mPCa) and mutations in certain DNA-repair associated genes, such as ATM and BRCA2[1,2].
- PARPi are effective in patients with mPCa and mutated BRCA2,with minimal activity in ATM mutations. ATR inhibitor combinations may target ATM mutations[3].
- Herein we investigate if distinct genomic characteristics between ATM-mutated, BRCA2-mutated, Homologous Repair Proficient (HRP), and Homologous Repair Deficient (HRD) patients with mPca, which may infer biomarkers for targeted therapeutics.

Objectives

- To define if the frequency distribution of alterations in prognostic markers (*TP53*), or presence of biomarkers of Immuno-Oncology (IO) and second-generation androgen receptor inhibitors (ARV7) differ in *ATM*-mutated, *BRCA2*-mutated, Homologous Repair Proficient (HRP), and Homologous Repair Deficient (HRD) patients with mPca .
- To correlate distinct patterns of alterations in known cancer-associated genes with these 4 subgroups

Methods

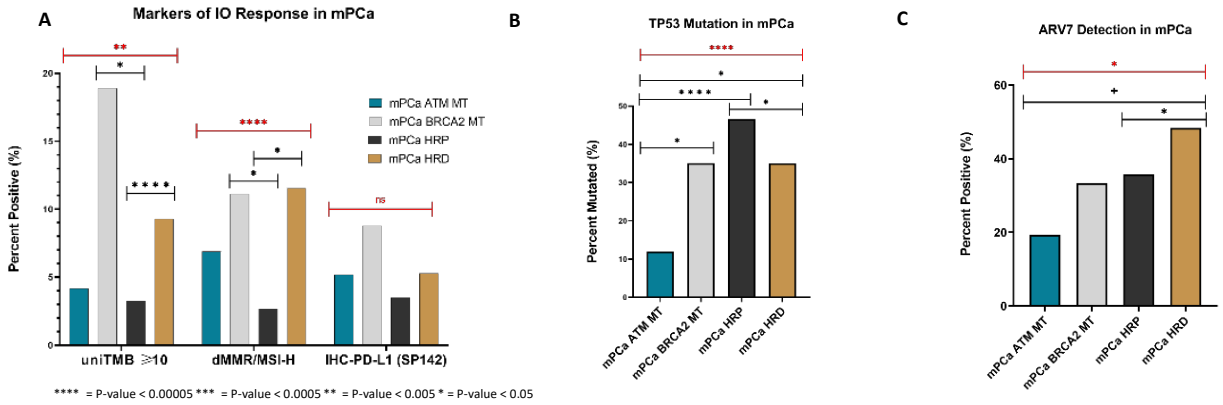
- 1375 cases of mPCa were included in the present study.
- Tumors were analyzed using next-generation sequencing (NGS), whole transcriptome sequencing (WTS), and immunohistochemistry (IHC) (Caris Life Sciences, Phoenix, AZ).
- The dMMR/MSI-H status was determined by IHC, NGS, and fragment analysis. Tumor mutational burden (TMB) was measured by counting all non-synonymous missense, nonsense, in-frame insertion/deletion and frameshift mutations found per tumor that had not been previously described as germline alterations.
- Statistical significance was determined using the χ^2 test and Benjamini-Hochberg method.

Results

Table 1. Patient demographics and tumor characteristics

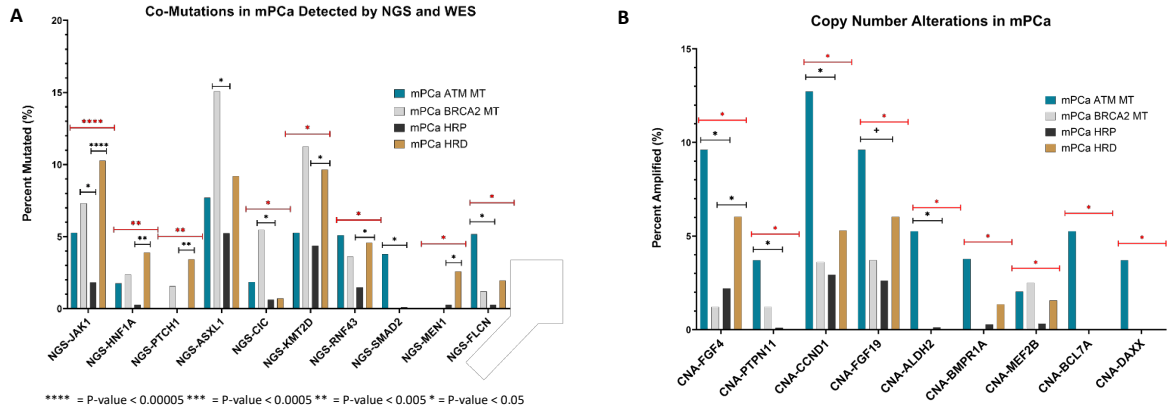
Characteristic	N	Median age, years (range)	Biopsy site (metastatic vs primary)	ATM-mutated. (N, %)	BRCA2-mutated (N,%)	HRP (N, %)	HRD
mPCa	2958	67 (35-90)	1375 (46.5%) vs 1583(53.5%)	59/1375 (4.2%)	84/1375 (6.18%)	1018/1375 (74.03%)	155/1375 (11.27%)

Figure 1. Differential biomarkers observed in ATM-mutated, BRCA2-mutated, HRP, and HRD mPCa, including IO predictors (A), TP53 mutations (B) and ARV7 (C)



**** = P-value < 0.00005 *** = P-value < 0.0005 ** = P-value < 0.005 * = P-value < 0.05

Figure 2. Differential Co-mutations (A) and Copy Number Alterations (B) in ATM mutant, BRCA2, HRP or HPD mPCa



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Conclusions

- *ATM*- and *BRCA2*-mutated mPCa are associated with differential features that may impact responses to immune or precision therapeutic strategies.
- *ATM*-mutated mPCa may have a less frequent rate of TP53 mutations and less prevalent ARV7 than the general population of HRD patients suggesting that ATR inhibitors, in combination with second generation androgen receptor inhibitors, may be a rational treatment option for this population.
- The clinical implications of enriched Folliculin (*FLCN*) mutations and Cyclin D1 (*CCND1*) amplifications in patients with ATM mutations and mPCa remain unclear and deserve further investigation.
- The associated mutational landscape also infers alternative targeted strategies for a subset of mPCa patients that harbor ATM or BRCA2 alterations.

Future Directions

- Multi–omic approaches may further characterize *ATM* and *BRCA2* loss in mPCa
- Novel therapeutic strategies that account for mechanistic differences between patient with *ATM*-mutated and other HRD mutation may improve outcomes in that population .

References

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3. Rodrigues DN, et al. Clin Oncol. 2020 Sep 20;38(27):3195-3204. PMID: 32568634