Truncal Drivers as Key Determinant of Treatment Outcomes in Concurrent High TMB and HRD Metastatic Prostate Cancers

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Background

PARP inhibitors (PARPi) are a promising treatment for prostate cancer with homologous DNA repair deficiencies (HRd), particularly in BRCA1/2 loss patients. However, 35-40% of these patients do not respond to PARPi. Our small case study identified three BRCA mutated HRd patients with high tumor mutation burden (TMBh) all responded well to immunotherapy but no response to PARPi, highlighting the need for a deeper genomic evaluation of metastatic prostate cancer (mPC) to understand the variations in clinical outcomes. We envision categorizing TMBh-HRd cases into two subsets: i) HRd truncal driver subset. ii) Mismatch Repair Deficient (MMRd) truncal driver subset. We hypothesize for highTMB-HRd cases, an accurate stratification of tumors based on their truncal driver status can be a precise predictor of their response to PARPi or immune checkpoint therapies

Methods

We analyzed high-quality exomes from 632 metastatic prostate cancer (mPC) patients, focusing on 43 DNA repair pathway genes. Our evaluation included TMB, MSI scores, and HRd signature scores. We distinguished between truncal and subclonal mutations using MESkit & supported our findings with CSMIC signature scores.

Results & discussion

In this analysis, we identified about 9% of mPC cases as TMB-high (≥10 mut/Mb, n=62), with 3% being MSI-high. A significant decrease in HRD-scar positivity ($p < 0.05$) was observed when we set a more conservative TMB threshold of ≥20 mut/Mb. Approximately 61% of tumors with TMB ≥20 were also MSI-high, with ~54% harboring MMR pathway gene aberrations and 61% are COSMIC MMRD signatures (+).

Notably, Of the 62 TMB-high cases, only 10 harbor BRCA gene mutations and additional 14 with BRCA gene mono allelic copy loss. Unsurprisingly, ~26%(16) of TMBh tumors were HRD signature-positive. Among the 10 BRCA-mutant tumors, 4 were MSI-high and TMB >20mut/Mb, but lacked HRD signatures, while the rest 6 HR signature positives tumors were TMB between 10-20 mut/Mb and were all MSI stable. Overall, ~45% of tumors with TMB between 10–20 mut/Mb were HRD-positive, whereas only 9% of tumors with TMB ≥20 were HRD-positive. We also observed a significant enrichment of ARSI resistance mutations in the TMB ≥20 prostate tumors (48%, $p < 0.00001$). Further analysis using GRITIC and MesKit inferred tumors with TMB ≥20 is truncally driven by MMR function aberration, with HRD possibly passenger events, making them less suitable for PARP inhibitors.

In conclusion, integrating multiparametric multisignature analysis alongside accurate DNA repair signatures or functional evaluation is crucial for tailored and precise treatment planning in high TMB-HRD patients with prostate cancer. Additionally, careful consideration should be given to highTMB patients regarding treating them with AR signaling inhibitors.

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Conflicts of Interest Disclosure Statement.

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