831 IMMUNE CHECKPOINT B7-H3 IS A THERAPEUTIC VULNERABILITY IN PROSTATE CANCER HARBORING PTEN AND TP53 DEFICIENCIES

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Background Prostate cancer is the most diagnosed cancer in men worldwide and the leading cause of cancer death in men worldwide. Checkpoint immunotherapy has yielded meaningful responses across many cancers but has shown modest efficacy in advanced prostate cancer. B7 homolog 3 protein (B7-H3/*CD276*) is an immune checkpoint molecule and has emerged as a promising therapeutic target. However, much remains to be understood regarding B7-H3's role in cancer progression, predictive biomarkers for B7-H3 targeted therapy, and combinatorial strategies.

Methods Genetic inactivation of *PTEN* and *TP53* is common in advanced prostate cancers. To identify PTEN- and p53-associated immune checkpoints, we performed multi-omics analyses of expression patterns of 51 checkpoint molecules in human prostate cancer samples. Then, we generated a novel generated genetically engineered mouse model to elucidate the role of B7-H3 in tumor development and progression of PTEN/p53-deficient prostate cancer. We also performed unbiased immunoprofling using Mass Cytometry (CyTOF) and Immunofluorescence to visualize B7-H3's impact on immune components in prostate tumors. In addition, we tested the B7-H3 inhibitor alone or in combination with other checkpoint blockades in preclinical models of castration-resistant prostate cancer (CRPC).

Results Our multi-omics analyses identified B7-H3 as one of the most abundant immune checkpoints in prostate tumors containing *PTEN* and *TP53* genetic inactivation. Here, we sought in vivo genetic evidence for, and the mechanistic understanding of, the role of B7-H3 in *PTEN*/*TP53* deficient prostate cancer. We found that loss of *PTEN* and *TP53* induced B7-H3 expression by activating transcriptional factor Sp1. Prostate-specific deletion of *Cd276* resulted in delayed tumor progression and reversed the suppression of tumor-infiltrating T cells and NK cells in *Pten*/*Trp53* genetically engineered mouse models. Furthermore, we tested the efficacy of the B7-H3 inhibitor in preclinical models of CRPC. We demonstrated that enriched regulatory T cells and elevated Programmed Cell Death Ligand 1 (PD-L1) in myeloid cells hinder the therapeutic efficacy of B7-H3 inhibition in prostate tumors. Finally, we showed that B7-H3 inhibition combined with blockade of PD-L1 or Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) achieved durable anti-tumor effects and had curative potential in *PTEN*/*TP53*-deficient CRPC model.

Conclusions Given that B7-H3 targeted therapies have been evaluated in early clinical trials, our studies provide new insights into the potential of biomarker-driven combinatorial immunotherapy targeting B7-H3 in prostate cancer, among other malignancies.

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Ethics Approval All mice were interbred and maintained at MD Anderson. All operations were performed according to the protocol after being reviewed and approved by MD Anderson's Institutional Animal Care and Use Committee (protocol #00001955).

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