555 CLINICAL AND PHARMACODYNAMIC BIOMARKER RESULTS FROM PORTER, A MULTI-COHORT PHASE 1 PLATFORM TRIAL OF COMBINATION IMMUNOTHERAPY FOR METASTATIC CASTRATION-RESISTANT PROSTATE CANCER PATIENTS

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Background Immune checkpoint therapy has failed to demonstrate a survival benefit for patients with metastatic castration resistant prostate cancer (mCRPC). New immunotherapy combination strategies are required to improve clinical outcomes in heavily-pretreated mCRPC patients.

Methods This open-label exploratory platform trial tested the safety and activity of immunotherapy combinations in patients with mCRPC. Three cohorts were enrolled A) bempegaldesleukin/nivolumab, B) stereotactic body radiation therapy (SBRT)/CDX-301 (FLT3L)/poly-ICLC/nivolumab, and C) CDX-301/INO-5151 (DNA vaccine encoding PSA/PSMA/IL-12)/nivolumab. Each cohort enrolled up to 15 participants who had progressed on androgen deprivation therapy with a subset being chemo- and/or radiation-exposed. Primary endpoint: safety. Secondary endpoints: composite response rate (CRR, defined as PR/CR per PCWG-3 modified RECIST v1.1, confirmed PSA reduction >50%, or CTC change from 5 to 4 cells/7.5 mL of blood), disease control rate (DCR; SD ≥6 mos), and time to radiographic PFS (rPFS). This study was not powered for comparison between cohorts.

Results Cohort A: CRR was 7% (1/14; 1 CTC response, no radiographic or PSA responses). DCR was 14% (2/14). Median rPFS was 2.8 months (95% CI: 2.0-7.3). Ten (71.4%) patients experienced a Grade 3-4 TRAE, including a Grade 5 TRAE of acute respiratory distress syndrome.

Cohort B: CRR was 33% (5/15; 1 PR, 1 CTC and 3 PSA responses, all in distinct patients). DCR was 27% (4/15). Median rPFS was 7.5 months (95% CI: 3.5-10.5). One (7%) patient experienced a Grade 3-4 TRAE.

Cohort C: CRR was 7% (1/14; 1 patient with both PR and PSA response). DCR was 14% (2/14). Median rPFS was 2.9 months (95% CI: 2.7-7.1). 2 (14%) patients experienced a Grade 3-4 TRAE.

Peripheral immune phenotyping analysis demonstrated distinct pharmacodynamic effects including increases in proliferating, activated T and NK cells following bempegaldesleukin treatment in cohort A. In cohorts B and C, the expansion of dendritic cells (DCs) and monocytes following FLT3L treatment was observed, as well as increases in serum proteins associated with DC activation/maturation. In cohort C, INO-5151 vaccination induced antigen-specific T cell responses. Elevated serum levels of PD-1 and IFN-gamma signaling-associated proteins were observed following nivolumab treatment in all cohorts.

Conclusions This platform study design demonstrated the feasibility and efficiency of iteratively testing distinct immunotherapy combinations with comprehensive biomarker assessment in patients with mCRPC. While neither cohort A nor C were expanded due to insufficient clinical activity, the clinical responses seen with SBRT/FLT3L/polyICLC/nivolumab suggest sufficient clinical benefit that may warrant additional investigation, particularly the contribution of radiation to the responses observed.

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Ethics Approval This study was approved by OHRP/FDA Parent Organization Number, IOG0000432 with the IRB registration number IRB00000533.

Consent Written informed consent was obtained from the patient for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

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