Background Immune checkpoint therapy has not provided meaningful clinical benefit in patients with metastatic castration-resistant prostate cancer (mCRPC). Biomarker-rich clinical trials offer the opportunity to identify molecular targets of response and resistance to potentially inform patient selection and novel combinations in future trials that improve anti-tumor responses in patients with mCRPC.

Methods Two cohorts of the biomarker-rich PORTER platform trial tested a backbone combination of CDX-301 [FLT3L] and nivolumab. Cohort B added treatments to enhance endogenous immunity (stereotactic body radiation therapy/polyICLC). Cohort C included INO-5151, DNA vaccine expressing PSA/PSMA/IL-12 DNA plasmids. Matched blood and tumor samples were collected longitudinally for extensive immune biomarker analyses using flow/mass and full spectrum flow cytometry, serum proteomics, DNA/RNA sequencing, and high-dimensional multiplex imaging. Immune cell composition and cell:cell interactions are being explored in the tumor microenvironment by CODEX imaging and correlated with peripheral biomarker findings of response. Candidate biomarkers were prioritized based on those that were associated with outcomes.

Results There were 7 participants (5 cohort B, 2 cohort C) with clinical benefit/response (rPR, DCR ≥6 months, PSA and/or CTC response) and 22 non-responders.

Prior to treatment, responders had lower frequencies of both naïve CD4 Thelper and CD8 T cells in the periphery, but more proliferating PD-1+ CD4 Thelper cells and T cells with effector and/or memory phenotypes (Tbet+ CD8 and Eomes+ CD4 Thelper cells). Additionally, responders had lower peripheral naïve B cell percentages but higher percentages of Tbet+ and memory B cells.

Prior to and on treatment, higher levels of LAMP3 protein in patients with clinical benefit from one cohort suggests a role for baseline and on-treatment differences in dendritic cell phenotypes. Further work to integrate these findings with tumor imaging and genomic data is ongoing. Overall, the joint analysis of the two cohorts involving FLT3L + nivolumab highlights the power of a platform study to rapidly identify common biomarkers of clinical response and/or resistance and simultaneously interrogate treatment effects of cancer-specific immunotherapy combinations.

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Trial Registration NCT03835533

Ethics Approval This study was approved by OHRP/FDA Parent Organization Number, IOG0000432 with the IRB registration number IRB0000533.

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.