BIOMARKER CORRELATES OF CLINICAL RESPONSE WITH FLT3L/NIVO BACKBONE TREATMENT IN THE MULTI-COHORT PHASE 1 PORTER PLATFORM TRIAL IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER PATIENTS

Kristin Skotts, Timothy Howes, Jia Yu, Julie Densmore, Diane Da Silva, Dinesh Kumar, Sandra Santulli-Marchito, Christopher Cabanici, Elaine Eisenbeisz, Geoffrey Iaciofano, Aaron Mayer, Tonnii Moore, Derek Jones, Kimberly Kapryan, Alex Dolgner, Richard Chen, Lisa Butterfield, Theresa LaVallee, Samantha Bucktrout, Lacey Padron, Ute Dugan, Michael Yellin, Tibor Keler, Jill O’Donnell-Tormey, Justin Fairchild, Lisa Salvador, Kristopher Wentzel, Lawrence Fong, Sumit Subudhi, Tina Bhardwaj, Karen Aujo, Matthew Galinsky, Parker Institute for Cancer Immunotherapy, San Francisco, CA, United States; Enable Medicine, Menlo Park, CA, United States; University of Pennsylvania, Philadelphia, PA, United States; Inovio Pharmaceuticals, Plymouth Meeting, PA, United States; Personalis, Menlo Park, CA, United States; Celldex Therapeutics, Hampton, NJ, United States; Cancer Research Institute, New York, NY, United States; Bristol Myers Squibb, Princeton, NJ, United States; The Angeles Clinic, Los Angeles, CA, United States; University of California San Francisco, San Francisco, CA, United States; MD Anderson, Houston, TX, United States; Mount Sinai Medical Center, New York, NY, United States; Memorial Sloan Kettering Cancer Center; New York, NY, United States

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 antitumor 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 (steroelectric body radiation therapy/polyIgLCL). 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 (pPR, 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 serum soluble proteins associated with cytotoxicity, inflammation, myeloid cell migration, cell adhesion, and immune response were observed in the responder group. LAMP3, a dendritic cell maturation marker, was elevated among patients with clinical benefit in cohort B.

Conclusions In this multi-cohort platform trial evaluating novel immunotherapy combination treatments in mCRPC, peripheral biomarkers associated with higher levels of proliferating, effector/memory B and T cells and inflammatory immune responses were found in patients with clinical benefit, both 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.

Acknowledgements We extend our gratitude to the patients, their families, the clinical investigators, and their site staff members who are making this trial possible. We would also like to thank Carri Browne, Christopher Perry, and Lancelote Leong at Parker Institute for Cancer Immunotherapy (PICI) for operations leadership of the trial. We thank Maria Jaimes and Quentin Low from Cytek Biosciences for spectral flow method development and sample analysis. We thank Jay Campbell (CRI), Samik Upadaya (CRI), Andres Salazar (OncoVir) and Silvia Boffo (BMS) for their contributions. We thank Bristol Myers Squibb (BMS), Celldex, Oncovir and Inovio for collaboration and study drugs. The study was funded by Cancer Research Institute, BMS and PICI.

Trial Registration NCT03835533

Ethics Approval This study was approved by OHPR/FDA Parent Organization Number, JG0000432 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.