IMMUNE CORRELATES FROM QUEST1 IN MEN WITH CASTRATION-RESISTANT PROSTATE CANCER

¹Nicole Toney*, ¹Yo-Ting Tsai, ²Jason Redman, ²James Gulley, ²Jeffrey Schlom, ²Renee Donahue. ¹National Institutes of Health, Bethesda, MD, USA; ²National Institutes of Health, Bethesda, MD, USA

Background Immune checkpoint inhibitors have limited efficacy in unselected metastatic castration-resistant prostate cancer (mCRPC) patients. Combination immunotherapy approaches to generate a tumor-directed immune response (vaccine) and facilitate the resulting anti-tumor immune activity (checkpoint inhibitors, cytokines) have shown synergy pre-clinically. In the phase I/II Quick Efficacy Seeking Trial (QuEST1, NCT03493945), combination of a brachyury-targeting vaccine (BN-brachyury), TGF- β /anti-PD-L1 blocking bifunctional fusion protein (bintrafusp alfa), and IL-15 superagonist (N-803) have produced preliminary evidence of efficacy in CRPC, with 5/12 patients having a sustained prostate-specific antigen (PSA) response that included 2 radiographic partial responses, compared to 1/13 patients who received BN-brachyury plus bintrafusp alfa. Here, we present immune correlates from patients enrolled in Arm 2.1A (BN-brachyury + bintrafusp alfa) and Arm 2.2A (BN-brachyury + bintrafusp alfa + N-803).

Methods Peripheral blood mononuclear cells (PBMC) and serum were obtained from 25 patients pre and multiple time points post treatment. PBMCs were assessed for antigen specific T cells targeting brachyury and MUC-1 by intracellular cytokine staining, 158 peripheral immune cell subsets by multicolor flow cytometry, and TCRV β sequencing. Patients were also evaluated for complete blood counts, and serum cytokines/soluble factors using ELISA assays and OLINK's immuno-oncology panel. Immune parameters were compared between Arm 2.1A and Arm 2.2A and evaluated for associations with clinical response in Arm 2.2A.

Results Brachyury and MUC-1 specific T cells were increased in most patients post treatment in both arms. A greater increase in total NK cells, refined NK subsets expressing markers of activation/adhesion, and TCR diversity was observed after 2 weeks of therapy in Arm 2.2A than Arm 2.1A. Absolute lymphocyte counts and serum levels of granzyme B, sCD27, and sCD40L were also increased after 2 weeks in Arm 2.2A compared to Arm 2.1A. Serum proteomic analyses revealed a greater increase in analytes related to NK cell signaling in Arm 2.2A than Arm 2.1A. Specific immune parameters at baseline associated with development of clinical response in patients treated in Arm 2.2A; responders had trends of higher frequencies of CD4+ and CD8+ T cells, lower frequencies of MDSCs and monocytes, and lower levels of serum IL-6 and sCD40 than non-responders.

Conclusions These findings demonstrate enhanced immune activation of both NK and T cells with the addition of N-803 in Arm 2.2A, where more clinical activity was observed than in Arm 2.1A. These findings support the continued evaluation of the combination of BN-brachyury, bintrafusp alfa, and N-803 in patients with mCRPC.

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Ethics Approval The trial was approved by the Institutional Review Board of the Center for Cancer Research, National Cancer Institute (ClinicalTrials.gov identifier: NCT03493945).

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