

Personalizing Combinatorial Prostate Cancer Immunotherapy

Russell Pachynski MD¹, Robert Schreiber PhD², Elaine Mardis PhD³, Jeff Ward MD PhD¹, Vivek Arora MD PhD¹, James Gulley MD PhD⁴

¹Division of Oncology, Department of medicine ²Department of Pathology and Immunology, Washington University School of Medicine, St Louis, MO; ³The Institute for Genomic Medicine, Ohio State University Comprehensive Cancer Center, Columbus, OH; ⁴Genitourinary Malignancies Branch, NCI/NIH, Bethesda, MD

Background: Despite the great advances made in the field of immunotherapy with checkpoint inhibitors, responses in prostate cancer remain suboptimal. The mutational burden of prostate cancer is relatively lower compared to tumor types in which these checkpoint inhibitors are approved (e.g. bladder, lung, melanoma). Recently, two large phase III clinical trials of metastatic prostate cancer patients treated with single agent anti-CTLA-4 checkpoint inhibition failed to show significant increases in overall survival, suggesting that combination immunotherapy is warranted in this patient population. Probstvac-VF Tricom is a therapeutic vaccine that incorporates the DNA for the shared self-antigen PSA into the vaccinia (or fowlpox) virus strain, with promising activity seen in phase II trials and an ongoing phase III trial. While Probstvac has shown promising results thus far, the use of vaccines containing a non-mutated self-antigen may also lead to suboptimal results, and ultimately must overcome pre-existing tolerance. Preclinical studies utilizing unique neoantigen vaccines have shown proof of principal ability to overcome immunoresistance, both alone and in combination with checkpoint inhibition, and ongoing human trials continue to evaluate their efficacy.

Methods: Here, we propose to optimize immunotherapy for patients with metastatic prostate cancer by combining checkpoint blockade with both shared antigen and personalized neoantigen vaccines in a clinical trial. By using chemotherapy and androgen deprivation therapy to initially treat high risk/high volume metastatic prostate cancer, we will optimally reduce the tumor burden in these patients – improving their ability to respond to immunotherapy. Patients will be evaluated for the production of personalized tumor neoantigen peptide vaccines based off a metastatic biopsy. We will then treat patients with Probstvac followed by personalized neoantigen vaccines, both in combination with ongoing checkpoint blockade. Pre- and post-treatment biopsies of tumor will be obtained. Serial PBMCs and plasma will be obtained throughout the trial. We hypothesize that the addition of checkpoint immunotherapy and personalized peptide vaccines will improve the anti-tumor immune response to a shared antigen vaccine, and enhance responses after initial immunoediting has occurred. Results from these studies will then be used to rapidly optimize immunotherapy treatment approaches and could be the basis for larger trials in order to study the impact on overall survival.

Results/Conclusions: Planned enrollment of 20 patients to establish safety/tolerability and evaluate immune responses.

Conflict of Interest: No relevant conflicts.

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