A PILOT TRIAL OF NEOANTIGEN DNA VACCINE IN COMBINATION WITH NIVOLUMAB/IPILIMUMAB AND PROSTVAC IN METASTATIC HORMONE-SENSITIVE PROSTATE CANCER

Russell K. Pachynski[1], Malachi Griffith[1], Jeff Ward[1], Vivek Arora[1], Will Gillanders[2], James Gulley[3], Robert Schreiber[4]

[1]Division of Oncology, Department of Medicine; [2]Department of Surgery [4]Department of Pathology and Immunology, Washington University School of Medicine, St Louis, MO, USA; [3]Genitourinary Malignancies Branch, NCI/NIH, Bethesda, MD, USA

Background:
Despite the great advances made in the field of immunotherapy with checkpoint inhibitors (CPI), responses in prostate cancer remain suboptimal. Recently, two large phase III clinical trials of metastatic prostate cancer patients treated with single agent anti-CTLA-4 (ipilimumab) CPI failed to show significant improvement in overall survival (OS). Prostvac-VF Tricom is a therapeutic vaccine that incorporates the DNA for the shared self-antigen PSA into the vaccinia (or fowlpox) virus strain. A large randomized phase III trial recently showed no improvement in OS compared to placebo. We hypothesized that strategies that combine immunotherapy with vaccination are needed for efficacy in this patient population, in order to overcome the pre-existing tolerance associated with non-mutated self-antigen vaccines. Preclinical studies utilizing unique neoantigen vaccines have shown the ability to overcome immunoresistance, both alone and in combination with CPI, and ongoing human trials continue to evaluate their efficacy.

Methods:
We are currently performing a clinical trial (NCT03532217) that combines ipilimumab + nivolumab with both shared antigen and personalized neoantigen vaccines in metastatic hormone-sensitive prostate cancer. Patients with high risk, high volume disease will be treated after initiation of chemotherapy and androgen deprivation therapy – potentially improving their ability to respond to immunotherapy at their tumor burden nadir. Patients are then treated with Prostvac-VF followed by personalized neoantigen vaccines, both in combination with ongoing checkpoint blockade. Planned total enrollment is for 20 patients between two sites (WU, NCI). We hypothesize that the addition of CPI and personalized neoantigen vaccines will improve the anti-tumor immune response to a shared antigen vaccine, and enhance responses after initial immunoediting has occurred.

Results:
We have enrolled 9 patients to date. The combination of Prostvac, ipilimumab, and nivolumab have been well tolerated with only grade 1-2 associated toxicities. Three patients to date have received personalized neoantigen vaccines produced from their metastatic tumor biopsies. No additional toxicities were seen with the addition of the neoantigen vaccine, which is delivered via electroporation. Preliminary increases in activation/co-stimulatory/co-inhibitory were seen after treatment with Prostvac/ipilimumab/nivolumab, suggesting immune priming. Sample collection and analyses are ongoing.

Conclusions:
Here, we present data from the first clinical trial evaluating a combination immunotherapy approach incorporating personalized neoantigen vaccines in the metastatic hormone-sensitive setting. The approach, to date, has been feasible with the first three patients able to generate and receive their neoantigen vaccines. Safety/tolerability to date has been reasonable with only grade 1-2 related adverse events. Preliminary data shows evidence of immune activation with the combination immunotherapy. Analyses to determine responses to the personalized neoantigen vaccines are ongoing.

COI: RKP has been on advisory boards for BMS. No other relevant conflicts.

Funding: Prostate Cancer Foundation Team Challenge Award 2016