

Combining Immune Checkpoint Inhibition (Ipilimumab and Nivolumab) with a Therapeutic Cancer Vaccine (Prostvac) in Prostate Cancer

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Background: To this point the clinical value of immune checkpoint inhibition in prostate cancer has been modest, with only one trial (pembrolizumab with enzalutamide) suggesting a clinical impact in approximately 20% of patients based on preliminary data (Graff et al, ESMO, 2016). The broader clinical experience includes two negative phase III trials with ipilimumab in metastatic castration resistant prostate cancer (mCRPC). One strategy to mobilize immune cells to the tumor microenvironment and make immune checkpoint inhibition a more relevant therapeutic option is to employ a therapeutic cancer vaccine to generate an antigen specific, anti-tumor response. A neoadjuvant study demonstrated this proof-of-concept using sipuleucel-T (Fong L. et al., JNCI, 2014). Prostvac represents an off the shelf alternative vaccine in the form of a pox-viral based strategy that targets PSA. Preliminary studies suggest a survival advantage in mCRPC (Kantoff et al., JCO 2010). An ongoing phase III trial is evaluating prostvac in mCRPC in larger study (NCT01322490). A previous phase II study also suggested clinical benefit of the combination of ipilimumab and prostvac in mCRPC, with a median overall survival >34 months, compared to approximately 26 months seen with prostvac alone in relatively concurrent studies (Madan et al., Lancet Oncol, 2012).

Methods: To evaluate the therapeutic potential of the combination of ipilimumab and nivolumab with prostvac, studies will be conducted in mCRPC (safety lead-in of 10 patients) and in the neoadjuvant setting. Once safety is confirmed in mCRPC, the plan is to evaluate prostvac individually with nivolumab and then with ipilimumab in sequential cohorts of 16 patients in the neoadjuvant setting prior to prostatectomy. A third cohort will combine all three immunotherapies in untreated patients prior to prostatectomy once safety is confirmed. The dosing of nivolumab is 240 mg (flat dose) and the dose of ipilimumab is 1 mg/kg. Patients will be treated for approximately 8 weeks prior to definitive surgery. The primary objectives of this study are to determine the safety of this combination and evaluate the immune infiltration of the tumor after the immunotherapy combinations. Peripheral immune responses will also be evaluated and compared to immunologic changes in the tumor seen after surgery and changes in PSA kinetics. This study is currently accruing at the National Cancer Institute in Bethesda, MD (NCT02933255).

Funding: NCI intramural funding. Immunotherapy is being supplied by Bristol Myers Squibb and Bavarian Nordic, respectively.

The authors have no financial conflicts of interest.