350 PHASE 2 TRIAL OF A DNA VACCINE WITH PEMBROLIZUMAB IN PATIENTS WITH METASTATIC, CASTRATION-RESISTANT PROSTATE CANCER (MCRPC)

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Background We previously reported a pilot clinical trial using a DNA vaccine encoding prostatic acid phosphatase (pTVG-HP), given over 12 weeks either concurrently or in sequence with pembrolizumab, in patients with mCRPC. We report here the final analysis of this trial following two additional treatment arms in which patients with mCRPC were treated beyond 12 weeks until progression.

Methods Patients with mCRPC were treated with pTVG-HP and pembrolizumab every 3 weeks (Arm 3, n=20), or pTVG-HP every 2 weeks and pembrolizumab every 4 weeks (Arm 4, n=20). The primary objectives were safety, 6-month PFS, median time to radiographic progression, and objective response rates. Secondary objectives included immunological evaluations.

Results Treatment was without unexpected toxicity, and only 1 grade 4 event (hyperglycemia) was observed. Immune related adverse events (irAE) > grade 1 included adrenal insufficiency, hepatitis, colitis, thyroid dysfunction, pancreatitis, pneumonitis, and rash, occurring in 42% of patients overall. 10/25 patients with measurable disease experienced any decrease in tumor volume from baseline, with 1 confirmed PR and no CR. 23/66 (35%) experienced any PSA decline from baseline. Overall median TTP was 5.4 months (95% CI; 5.3–8.1 months); median TTP for Arm 3 was 5.3 months compared to 8.0 months for Arm 4. Overall, 41.7% of patients had no radiographic progression at 6 months (29.9% Arm 3, 57.9% Arm 4). Median overall survival was 22.9 months. IFNγ and/or granzyme B immune response to PAP was detected in 2/20 patients in Arm 3 and 6/20 patients in Arm 4. Cytokines associated with immune activation and CD8+ T cell recruitment were augmented in the plasma of patients at weeks 6 and 12. Increased IFNγ in the sera at week 6 trended with prolonged TTP (p=0.010) and overall survival (p=0.025). The development of irAE was associated with a prolonged TTP (HR=0.25, p=0.003).

Conclusions PD-1 pathway inhibitors have demonstrated little clinical activity to date as monotherapies for mCRPC. Our findings demonstrate that combining PD-1 blockade with tumor-targeted T-cell activation using pTVG-HP is safe, can augment tumor-specific T cells, and result in objective changes with longer time to progression than what has been observed in previous trials. The association of progression or survival with increased IFNγ, irAE, and vaccine schedule suggests T cell activation by vaccination is critical to the mechanism of action of this combination. This study suggests this approach should be further evaluated in randomized clinical trials for patients with advanced mCRPC.

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Trial Registration NCT02499835

Ethics Approval This trial was reviewed and approved by the University of Wisconsin Human Subjects' Review Committee (IRB), protocol 2015–0453. All participants provided IRB-approved written informed consent before taking part.