

# Combination of vaccine and immune checkpoint inhibitor is safe with encouraging clinical activity

Ravi A. Madan, Christopher R. Heery and James L. Gulley\*

Laboratory of Tumor Immunology and Biology; National Cancer Institute; Bethesda, MD USA

**Keywords:** PROSTVAC, PSA-TRICOM, ipilimumab, vaccine, prostate cancer

This commentary provides the authors' perspective on the article "Ipilimumab and a poxviral vaccine targeting prostate-specific antigen in metastatic castration-resistant prostate cancer: a phase 1 dose-escalation trial", which has recently been published in *The Lancet Oncology*.

We recently published the results of a Phase I dose-escalation trial combining ipilimumab (anti-CTLA-4) and the PSA-TRICOM (PROSTVAC) vaccine.<sup>1</sup> Sipuleucel-T was the first therapeutic cancer vaccine to receive US Food and Drug Administration (FDA) approval after demonstrating an overall survival (OS) benefit compared with placebo control in patients with metastatic castration-resistant prostate cancer (mCRPC). The promise of clinical benefit with cancer vaccines was bolstered by this positive result and subsequent approval,<sup>2</sup> and indicated that endpoints commonly used in standard cancer therapies, such as progression-free survival (PFS), may not be ideal for evaluating cancer vaccines.<sup>3</sup> Indeed, it appears that the immune response develops over time and is sustained after treatment is completed, resulting in prolonged OS but not improved PFS. Similar results were seen in a multicenter Phase II randomized trial of PSA-TRICOM, which demonstrated an 8.5-mo improvement in median OS, as compared with placebo ( $p = 0.006$ ), despite a lack of improvement in PFS.<sup>4</sup> PSA-TRICOM is now being investigated in a Phase III trial.

CTLA-4 on T cells binds to CD80 (B7) on antigen-presenting cells, and attenuates the immune response after T-cell activation as part of the body's own means of regulating immune responses.<sup>5</sup> Ipilimumab, a monoclonal antibody

directed against CTLA-4, can inhibit such a negative regulatory signal, and potentially create more robust T-cell responses and higher-avidity antitumor T cells.<sup>6</sup> Ipilimumab was approved for treatment of metastatic melanoma by the FDA, based on improved OS for patients receiving this treatment compared with an active control.<sup>7</sup> Combining anti-CTLA-4 with PSA-TRICOM potentially provides directed T-cell activation, while allowing those activated T cells to kill tumor cells owing to diminished inhibitory signals.

The recently reported Phase I trial<sup>1</sup> was undertaken to determine if the combination of PSA-TRICOM (which induces positive co-stimulation) and ipilimumab (which blocks negative co-stimulation) in patients with mCRPC would lead to increased adverse events over what was expected from ipilimumab alone, whose known toxicities include autoimmune colitis, rash, hypophysitis, hypothyroidism and adrenal insufficiency.<sup>7</sup> A priming dose of  $2 \times 10^8$  plaque-forming units (PFU) of recombinant vaccinia (rV)-PSA-TRICOM was given to all patients on day 1. Cohorts 1 to 4 received ipilimumab as a 90 min intravenous infusion at 1, 3, 5 and 10 mg/kg respectively, in combination with  $1 \times 10^9$  PFU of recombinant fowlpox (rF)-PSA-TRICOM on day 15 of cycle 1, then every 28 days (Fig. 1). The trial was initially designed to give 6 doses of ipilimumab

and then continue with monthly vaccine courses if patients had stable disease, but an amendment allowed for 4 additional doses of ipilimumab.

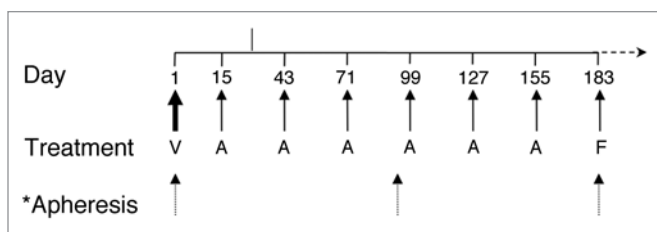
For the 30 patients enrolled, the combination of PSA-TRICOM and ipilimumab had a similar toxicity profile to that described with ipilimumab alone, with increased incidence of autoimmune endocrinopathies at the 5 and 10 mg/kg doses and colitis at all doses higher than 1 mg/kg. Rash was also common, in particular at the dose of 10 mg/kg. The maximum tolerated dose was not exceeded. Additional hypothesis-generating data were presented.

At the midpoint of dose level 2, the protocol was amended to enroll only chemotherapy-naïve patients to maximize the immune effect.<sup>8</sup> Only 1 out of 6 patients who had previous chemotherapy had a PSA decline. Of the remaining 24 chemotherapy-naïve patients, 58% ( $n = 14$ ) had PSA declines and 25% ( $n = 6$ ) had PSA declines  $\geq 50\%$ . Both these findings represent substantial ameliorations as compared with previous studies employing PSA-TRICOM alone.<sup>4,9</sup> There was no evidence of anti-PSA antibodies to explain the decrease in PSA values. Autoimmune endocrinopathy (e.g., adrenal insufficiency) was a potential confounder that may have been responsible for PSA declines, but 2 patients with PSA declines  $\geq 50\%$  experienced no autoimmune endocrinopathy. Of 12 patients with measurable disease, 3 had

\*Correspondence to: James L. Gulley; Email: gulleyj@mail.nih.gov

Submitted: 04/11/12; Accepted: 05/02/12

<http://dx.doi.org/10.4161/onci.20591>



**Figure 1.** Schematic representation of dosing schedule on trial. V, PROSTVAC-V/TRICOM (vaccinia) × 1 dose + sargramostim daily × 4 doses (no ipilimumab); A, PROSTVAC-F/TRICOM (fowlpox) × 1 dose + ipilimumab × 1 dose + sargramostim daily × 4 doses; F, PROSTVAC-F/TRICOM (fowlpox) × 1 dose + sargramostim daily × 4 doses (no ipilimumab).

unconfirmed partial responses. There was no significant difference in OS among the cohorts attributable to the dose of ipilimumab. Median OS for all patients was 34.4 mo (95% CI: 29.6 to > 41), with a 2 year OS of 73% (95% CI: 55.6 to 85.8). In the 24 chemotherapy-naïve patients, 3 year OS was 52.6% (95% CI: 31.4 to 72.9). After a median potential follow-up of 48.5 mo, median OS has not yet been reached.

Peripheral blood mononuclear cells from HLA-A2<sup>+</sup> patients were tested by

an enzyme-linked immunosorbent spot (ELISPOT) assay to measure immunologic responses (PSA-specific T cells). Of the three patients evaluable at the highest dose level, two had increased responses to PSA post-treatment and one had PSA-specific T cells pre- and post-treatment. Although not explicitly targeted by the vaccine, some patients generated T cells specific for additional tumor-associated antigens post-treatment. This finding is likely attributable to the previously

described phenomenon of the so-called “antigen cascade”, in which patients develop immune responses to antigens found on tumor cells, but not found in the vaccine, through cross-priming during T-cell killing.<sup>10</sup> Overall, 6 of 9 evaluable patients had enhanced antigen-specific T-cell responses.

This trial demonstrated that the combination of 10 mg/kg of ipilimumab plus a vaccine with substantial positive costimulation (PSA-TRICOM) does not worsen toxicity compared with ipilimumab alone. Additionally, the secondary data suggest that the median OS of patients treated with this combination (34.4 mo) may be superior to vaccine therapy alone (26 mo).<sup>2,4</sup> While this trial was not randomized, OS in chemotherapy-naïve patients is greater than would be expected in a historically similar patient population and provides the rationale for a larger randomized clinical trial to determine the efficacy of combining checkpoint inhibition with PSA-TRICOM vaccine.

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