

# An update on TroVax<sup>®</sup> for the treatment of progressive castration-resistant prostate cancer

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**Abstract:** Prostate cancer is a common human malignancy with few effective therapeutic options for treating advanced castration-resistant disease. The potential therapeutic effectiveness of immunotherapy and vaccines, in particular, has gained popularity based on the identification of prostate-associated antigens, potent expression vectors for vaccination, and data from recent clinical trials. A modified vaccinia Ankara (MVA) virus expressing 5T4, a tumor-associated glycoprotein, has shown promise in preclinical studies and clinical trials in patients with colorectal and renal cell carcinoma. This review will discuss the rationale for immunotherapy in prostate cancer and describe preclinical and limited clinical data in prostate cancer for the MVA-5T4 (TroVax<sup>®</sup>) vaccine.

**Keywords:** castration resistance, prostate cancer, TroVax, vaccine

## Introduction

Prostate cancer is the second most common malignancy and the sixth most common cause of cancer-related mortality worldwide.<sup>1</sup> The natural history of early diagnosed clinically localized prostate cancer is indolent in the majority of men, with up to 80% having 20-year progression-free survival without local treatment.<sup>2</sup> The men who develop advanced-stage disease, characterized by distant metastasis, initially undergo a hormone-sensitive period of growth when tumor cell proliferation is dependent on androgen stimulation. The use of androgen deprivation therapy (ADT) is beneficial during this stage of the disease, but management becomes more challenging as tumors evolve to become hormone refractory. New therapeutic options are needed, especially for patients with hormone-resistant tumors.

The terms “hormone-refractory prostate cancer” or “castration-resistant prostate cancer” (CRPC) are used interchangeably to describe prostate adenocarcinoma that progresses despite ADT, resulting in serum testosterone levels below a certain threshold, typically 20–50 ng/dL.<sup>3</sup> The definition of when a patient becomes castration resistant can vary and has a distinct impact on the expected median survival. Although, historically, median survival of 12–18 months could be expected for men with CRPC,<sup>4</sup> a more contemporary report using the first biochemical evidence of progression as the starting point quotes median survivals of 40–68 months, depending on the presence or absence of skeletal metastasis.<sup>5</sup> Elevated serum prostate-specific antigen (PSA), lactate dehydrogenase, and alkaline phosphatase, as well as the presence of visceral metastasis, anemia, and low performance status, have been shown to portend decreased survival in these men.<sup>6</sup>

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Although there exists heterogeneity in defining survival, progression in CRPC is perhaps more prone to variability.<sup>7,8</sup> The Response Evaluation Criteria In Solid Tumors (RECIST) measure progression radiographically with solid tumor dimensions, but they do not take into account bone scan-detected lesions, abnormal biochemistry, or the quality of life manifestations of metastatic prostate cancer.<sup>9</sup> The Prostate Cancer Working Group (PCWG) was created in an effort to define clinical trial endpoints that are more specific for prostate cancer, and has expanded the definitions of progression to include quality of life and PSA levels.<sup>10</sup>

Using any definition, the situation remains that there are few effective therapeutic options for CRPC. Several cytotoxic medications have been studied, with docetaxel, which is currently the first-line therapy, demonstrating a statistically significant (but clinically modest) benefit in PSA response, pain control, improvement in quality of life, and increased median survival.<sup>11,12</sup> The TAX 327 trial reported that docetaxel every 3 weeks produced a 2.4-month increased median survival over mitoxantrone and had a 0.76 hazard ratio (HR) for death. Subsequent trials with satraplatin failed to demonstrate any benefit over placebo,<sup>13</sup> and the addition of gemcitabine to docetaxel failed to show any benefit over docetaxel alone.<sup>14</sup> Recently, cabazitaxel has shown to have significant activity against CRPC in a Phase III trial. Carbazitaxel extended both median and progression-free survival in men who either progressed during or completed a docetaxel-based treatment regimen compared with mitoxantrone.<sup>15</sup> Abiraterone acetate, a hormonal agent that irreversibly inhibits CYP17, has shown antitumor activity in docetaxel-treated patients in a Phase II trial.<sup>16</sup> Recent Phase III data indicate that this agent provides a PSA response as well as a 3.9-month survival benefit ( $P < 0.001$ ) over placebo.<sup>17</sup> These promising results will likely lead to US Food and Drug Administration (FDA) approval of this agent in the near future. Additional classes of agents currently undergoing study in CRPC include inhibitors of angiogenesis, growth factors, and endothelin. A comprehensive review of these agents may be found in a recent review by Nabhan et al.<sup>18</sup>

The role the immune system plays in tumor progression and containment is a topic of intense study and has provided a variety of therapeutic strategies for many cancers, including CRPC. Case reports of spontaneous regression of both liquid and solid human malignancies have supported hypotheses of antitumor host immune surveillance, and more recent experimental data in murine models have confirmed that tumor immune surveillance is mediated by cytotoxic lymphocytes and interferon- $\gamma$  production.<sup>19</sup> Further evidence supporting

the potential for immunotherapy against human tumors comes from data on interleukin 2 (IL-2), a cytokine that is critical to the maturation and proliferation of natural killer (NK), CD4+, and CD8+ T lymphocytes. In murine models of human renal cell, gastric, and squamous cell carcinomas, IL-2 was found to directly inhibit tumor growth via IL-2 receptors expressed by tumor cells as well as indirectly through activation of antitumor host NK and T cell responses.<sup>20</sup> High-dose IL-2 and recombinant interferon- $\alpha$  have shown clinical efficacy in metastatic melanoma and renal cell carcinoma (RCC) and in the adjuvant therapy of stage III melanoma, respectively. High-dose IL-2 can induce durable complete responses in a small but consistent subset of patients.<sup>21</sup> Furthermore, the combination of IL-2 with adoptive T lymphocytes has shown remarkable activity in metastatic melanoma, especially in the setting of host lymphodepletion.<sup>22</sup> The importance of T lymphocytes in the development of metastasis has also been suggested in the murine melanoma model in which CD8+ T cell-depleted mice had reduced disseminated tumor cell dormancy.<sup>23</sup>

## Prostate immunotherapy

The identification of tumor-associated antigens in prostate cancer cells provides the basis for development of antigen-specific vaccination as a therapeutic approach to prostate cancer. Immunotherapy for prostate cancer has increasingly moved to the forefront of study for CRPC since the FDA approval of sipuleucel-T (APC8015) in April 2010. Sipuleucel-T (Provenge<sup>®</sup>, Dendreon, Seattle WA) consists of autologous dendritic cells loaded with prostatic acid phosphatase linked to granulocyte-macrophage colony-stimulating factor (GM-CSF). Phase III data from three trials demonstrated a survival benefit of approximately 4 months compared with placebo.<sup>24-26</sup> Another strategy in development utilizes a poxvirus prime/boost vaccine regimen wherein the viruses express the transgenes for PSA. In this strategy, a recombinant vaccinia virus encoding PSA is used as a priming vector, followed by boosting with recombinant fowlpox virus encoding PSA. Phase II data in patients with PSA recurrence after local therapy for prostate cancer and no evidence of metastatic disease reported a 45% freedom from PSA progression at 19 months. In addition, 46% of the men treated with the prime/boost vaccine regimen had an increase in PSA-reactive T cells, without evidence of an anti-PSA humoral response.<sup>27</sup> Subsequently, in an effort to increase the potency of the T cell response, several T cell costimulatory molecules were added to the poxviral vectors, including B7.1, ICAM-1, and LFA-3 (designated TRICOM

[triad of costimulatory molecules]).<sup>28</sup> In a Phase II study of men with CRPC, this vaccine system, PROSTVAC-VF<sup>®</sup> (BN ImmunoTherapeutics, Inc., Mountain View, CA), increased median overall survival by 8.5 months over a control vector treatment group.<sup>29</sup> These encouraging results need to be validated in a larger Phase III trial. Additional tumor-associated antigens undergoing early development include prostate-specific membrane antigen,<sup>30</sup> prostate stem cell antigen, and six-transmembrane epithelial antigen of the prostate.<sup>31</sup> Clinical trial data have yet to be reported with these antigens.

The immune response is highly regulated, and T cell activation is subject to homeostatic control through a series of costimulatory and coinhibitory molecules. Following engagement of the T cell receptor with its cognate peptide and major histocompatibility complex, the T cell receives a “second” or costimulatory signal through CD28, which binds to B7.1 and B7.2 on antigen-presenting cells. This second signal results in T cell proliferation and cytokine production. Shortly after activation, the cytotoxic T lymphocyte antigen 4 (CTLA-4) is mobilized to the cell surface and binds to B7.1 and B7.2 with higher affinity than CD28. CTLA-4 serves as a coinhibitory receptor, as signaling through CTLA-4 results in decreased cytokine production and inhibition of cell cycle stimulation. This provides a highly coordinated homeostatic mechanism for brief activation of T cells while avoiding prolonged stimulation and induction of autoimmunity. This pathway has also provided another approach for cancer immunotherapy. A human monoclonal antibody that targets CTLA-4 (ipilimumab) results in a blockade of the coinhibitory signaling mediated by CTLA-4 and allows T cells to remain in an activated state for a longer period of time. In a recent three-arm randomized Phase III clinical trial, patients receiving ipilimumab alone (3 mg/kg) or administered with a gp100 peptide vaccine were compared with patients receiving gp100 peptide vaccine alone.<sup>32</sup> Ipilimumab alone resulted in a significant improvement in overall survival compared with vaccine alone (10.1 months vs 6.4 months, HR for death 0.66,  $P = 0.003$ ), and ipilimumab in combination with gp100 vaccine also demonstrated an improved overall survival when compared with vaccine alone (10.0 months vs 6.4 months, HR for death 0.68,  $P < 0.0001$ ).<sup>32</sup> This trial also reported a 10%–15% grade 3 or 4 toxicity rate largely related to autoimmune events, including 14 (2.1%) mortalities, largely attributed to autoimmune colitis. Based on the results of this trial, the FDA approved ipilimumab for the treatment of metastatic melanoma in March 2011. Ipilimumab is also being studied in prostate cancer. In a Phase I clinical trial, 24 patients with CRPC were treated with ipilimumab in a dose escalation

manner (range 0.5–3 mg/kg) administered with subcutaneous GM-CSF. Treatment resulted in PSA responses in three of six patients treated at the highest dose level, and one patient had a partial response of visceral metastases.<sup>33</sup>

Allogeneic whole cell vaccines have also been studied in CRPC and offer the advantage of not needing to define specific antigens for vaccination. The GVAX platform utilizes irradiated allogeneic whole tumor cells transfected with the human GM-CSF gene. Although this agent showed PSA-stabilizing activity in Phase I/II trials, two Phase III clinical trials were terminated early due to excessive mortality in the experimental treatment arm.<sup>34</sup> The reason for this unexpected result is unclear, and further investigation will be needed to define the utility of this agent for CRPC.

## The 5T4 antigen

Fetal placental tissue evades immunosurveillance and invades “host” tissues, which is biologic behavior also displayed by neoplasms. Oncofetal antigens have therefore been the subject of study as possible diagnostic or therapeutic targets for human cancers. 5T4 is a 72kD protein identified on the syncytiotrophoblastic epithelium of human placental tissue using a murine monoclonal antibody.<sup>35</sup> 5T4 is a cell surface glycoprotein that is expressed on a variety of human tumors, including breast, ovary, stomach, colorectal, nonseminomatous testis, bladder, and clear cell RCC, whereas expression is absent on most normal human tissues and weak on some normal epithelia.<sup>36</sup> In contrast to PSA, 5T4 is not cleaved and is typically not found circulating in the serum. In vitro studies demonstrated that cells transfected with 5T4 cDNA had disrupted cell–cell contact and increased motility, suggesting a role for this molecule in tumor metastasis.<sup>37</sup> This was further supported by data demonstrating that increased 5T4 expression was correlated with tumor invasiveness in a variety of human cancers.<sup>38–40</sup> 5T4 is strongly expressed on the surface of most prostate adenocarcinoma cells. Thus, 5T4 is an ideal antigenic target, as 5T4 exhibits selective tumor cell expression, may be required for tumor progression, and does not exist in soluble (and potentially immunosuppressive) forms.

## Modified vaccinia virus Ankara (MVA)

Modified vaccinia Ankara (MVA) is a vaccinia virus attenuated by multiple passages through chick embryo fibroblasts.<sup>41</sup> MVA is attractive as a viral vector due to its proven safety record as an alternative vaccine against smallpox in immunosuppressed hosts. In addition, it has poor replication in transformed human cell lines with limited cell–cell spread,

in part due to potent induction of type I interferon from human cells.<sup>42</sup> Pox viruses such as MVA can be engineered to encode large amounts of transfected DNA, and provide immunogenicity due to the expression of a soluble IL-1- $\beta$  receptor.<sup>43</sup> The MVA vector was used to encode human 5T4 for vaccination purposes and extensively evaluated in preclinical and clinical settings.

## MVA-5T4 preclinical data

Recombinant MVA-expressing human 5T4 (MVA-h5T4; TroVax<sup>®</sup>, Oxford Biomedica, Oxford, UK) has shown both protective and therapeutic effects against tumors in murine models. Mice inoculated with three doses of MVA-h5T4 developed humoral responses to h5T4. When these mice were challenged with B16-5T4 melanoma and CT26-5T4 colorectal tumor cells, they had significantly fewer lung tumor nodules than the mice inoculated with vaccine and treatment controls (MVA-LacZ or phosphate buffered saline [PBS]).<sup>44</sup> In an experiment designed to test MVA-5T4 for treatment efficacy against established tumors, mice were first injected with CT26-5T4 tumors then immunized with two doses of MVA-5T4. The mice treated with MVA-5T4 had a reduction in tumor burden compared with the MVA-LacZ- or PBS-treated controls.<sup>44</sup> Interestingly, these experiments did show an immunoglobulin G antibody-mediated response, but there was no evidence of a CTL response.<sup>44</sup> In a follow-up study using the CT26 tumor model, mice depleted of CD8+ T lymphocytes showed no reduction in antitumor effect mediated by MVA-5T4, whereas mice depleted of CD4+ T lymphocytes had a completely abrogated response. This suggested that the treatment effect of MVA-5T4 was CD4+ T cell dependent and antibody mediated.<sup>45</sup>

## MVA-5T4 clinical data

Table 1 summarizes the clinical and immunologic results of clinical trials using TroVax<sup>®</sup> to date. TroVax<sup>®</sup> was administered to 22 patients with metastatic colorectal cancer in a Phase I trial that established its safety and immunogenicity. Fourteen of 17 evaluable patients had a measurable 5T4-specific antibody response, and eight patients had a de novo 5T4-specific cellular proliferation response.<sup>46</sup> 5T4-specific antibody titers significantly predicted time to progression but not overall survival ( $P = 0.08$  for all patients and  $P < 0.05$  in those who mounted a 5T4 antibody response).<sup>46</sup> Although 50% of the patients did have injection site erythema, there were no serious adverse events attributable to TroVax<sup>®</sup>.<sup>46</sup> These encouraging results supported the initiation of Phase II trials of TroVax<sup>®</sup> for cancer immunotherapy.

TroVax<sup>®</sup> was further evaluated in three Phase II trials for metastatic colorectal cancer. In the first study, MVA-5T4 monotherapy was administered before and after surgical metastasectomy. There were no serious adverse events, and the serologic and cellular response rates were similar to those in the Phase I trial.<sup>47</sup> Although this study was not designed to prospectively determine survival, a retrospective analysis found a correlation between 5T4 cellular proliferative responses and survival.<sup>47</sup> Two trials combined MVA-5T4 with multiagent chemotherapy, and both reported an increased magnitude and duration of 5T4-specific immune responses compared with the earlier trials.<sup>48,49</sup> One trial found a significant correlation between 5T4 cellular response and progression based on RECIST criteria.<sup>50</sup> These trials not only established the safety of the concurrent administration of multiagent chemotherapy but also suggested a benefit compared with MVA-5T4 monotherapy after chemotherapy.

TroVax<sup>®</sup> has been extensively evaluated in patients with metastatic RCC. Three Phase II studies and one multi-institutional, randomized, prospective Phase III trial for metastatic RCC have combined TroVax<sup>®</sup> with low- and high-dose IL-2, interferon- $\alpha$ , and the multityrosine kinase inhibitor sunitinib. Collectively, these trials reported favorable safety data similar to the colorectal cancer trials.<sup>51-55</sup> All of the Phase II trials found a significant association between 5T4-specific antibody responses and overall survival, and the low-dose IL-2 and TroVax<sup>®</sup> trial also reported an association between anti-5T4 antibody response and progression-free survival.<sup>51,53,54</sup>

TRIST (TroVax<sup>®</sup> Renal Immunotherapy Survival Trial) was the first Phase III study designed to establish the efficacy of TroVax<sup>®</sup> (MVA-5T4) in patients with RCC. In this study, patients were treated with IL-2, interferon- $\alpha$ , or sunitinib, according to investigator preference, and patients were then randomized to additional therapy with TroVax<sup>®</sup> or placebo. The vaccine was well tolerated but did not result in enhanced overall survival relative to placebo controls.<sup>55</sup> However, several subgroup analyses were performed that identified patients for whom MVA-5T4 may be of benefit. Specifically, patients with a favorable prognostic score receiving MVA-5T4 and IL-2 had a survival benefit relative to placebo and IL-2 (HR 0.54).<sup>55</sup> Furthermore, this study reconfirmed the Phase II finding that high anti-5T4 antibody responses are associated with improved survival.<sup>55</sup> Another interesting finding was a trend toward improvement in survival for patients with a specific immune response surrogate score that included the 5T4-specific antibody titer, hemoglobin level, and hematocrit.<sup>56</sup> This was developed by assessing various host parameters in 590 patients treated on the Phase III TRIST

**Table 1** Clinical trials using TroVax®

Trial	Disease	Phase	n	Concomitant agent(s)	Control	5T4 Immunological response rate		Clinical response	Other conclusion(s)
						Antibody	Cellular		
Harpop et al. Clin Cancer Res. Jun 2006	CRC	I/II	22	None	None	14/17 (82%)	16/17 (94%)	5/17 (29%)	5T4 antibody levels correlated to TTP ( $P < 0.01$ )
Elkord et al. J Immunother. Nov 2008	CRC	II	20	None	None	18/19 (95%)	13/20 (65%)	Not reported	5T4 antibody response in survivors (weeks 2 to 14) was 4-fold greater compared with those with early deaths ( $P = 0.058$ ). Peritumoral CD3 infiltration associated with prolonged survival ( $P = 0.012$ ) 5T4-specific cellular response not correlated with clinical response. Median OS 15.4 months
Harpop et al. Cancer Immunol Immunother. Jul 2008	CRC	II	19	5-FU, leukovorin, irinotecan	None	10/12 (83%)	10/12 (83%)	6/8 (75%) with >50% reduction in CEA, PR in 6/12 (50%), CR in 1/12 (8%)	5T4-specific cellular response not correlated with clinical response. Median OS 15.4 months
Harpop et al. Clin Cancer Res. Aug 2007	CRC	II	17	5-FU, folinic acid, oxaliplatin	None	10/11 (91%)	9/11 (82%)	7/11 (64%) with >50% reduction in CEA, PR in 5/11 (45%)	Significant correlation between 5T4-specific cellular response and RECIST PR. ( $P = 0.006$ )
Kaufman et al. J Transl Med. Jan 2009	RCC	II	25	IL-2 (high dose)	None	25/25 (100%)	13/23 (57%)	No objective PR. 12/23 (52%) with stabilization	Median PFS 4.8 months. Patients with stable disease exhibited an increase in the effector to regulatory T cell ratio that persisted for at least 24 months and 50% reduction in the mean number of Tregs within four weeks of completing the first course of IL-2 ( $P = 0.006$ )
Hawkins et al. J Immunother. May 2009	RCC	II	11	IFN-alpha	None	11/11 (100%)	5/11 (45%)	No objective PR	Identified 5T4-specific CTLs, induced by TroVax vaccination, which are capable of secreting both IFN[gamma] and perforin in response to antigenic stimulation. Median TTP 9 months 5T4 antibody response correlated with longer PFS and OS
Amato et al. Clin Cancer Res. Nov 2008	RCC	II	25	IL-2 (low dose)	None	21/25 (84%)	5/11 (45%)	Objective response 3/25 (12%), stabilization 6/25 (24%)	No significant difference in PFS or OS. Addition of IFN-[alpha] to MVA-5T4 did not impact 5T4-specific immune responses
Amato et al. J Immunother. Sep 2009	RCC	II	28	IFN-alpha (n = 15)	TroVax alone (n = 13)	21/25 (84%)	7/21 (33%)	Disease stabilization in 14 patients: MVA-5T4 plus IFN-[alpha] (n = 7) vs MVA-5T4 alone (n = 7). No difference in PR in clear cell histology patients	OS equivalent (median 20.1 months MVA-5T4 versus 19.2 months placebo; $P = 0.55$ ). CR (MVA-5T4, n = 2; placebo, n = 5), PR (MVA-5T4, n = 47; placebo, n = 46), stable disease in 164 (44.9%) MVA-5T4-treated patients and 173 (47.1%) placebo-treated patients
Amato et al. Clin Cancer Res. Nov 2010	RCC	III	733	Sunitinib, IL-2, IFN-alpha (n = 365)	Placebo (n = 368)	56% in MVA-5T4 patients vs 6% placebo	Not reported		5T4 antibody response correlated with improved OS. Good prognosis (MSKCC 0) with MVA-5T4 plus IL-2 improved OS compared to placebo plus IL-2 (HR, 0.54; $P = 0.046$ ).

(Continued)

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Trial	Disease	Phase	n	Concomitant agent(s)	Control	5T4 Immunological response rate		Clinical response	Other conclusion(s)
						Antibody	Cellular		
Amato et al. J Immunother. Aug 2008	CRPC	II	27	GM-CSF (n = 13)	TroVax alone (n = 14)	24/24 (100%)	8/24 (33%)	Reduced rate of PSA change: TroVax alone (n = 4) or TroVax+GM-CSF (n = 2). No objective responses on imaging. TTP in the TroVax alone arm (4.05 mo) compared with TroVax+GM-CSF (2.1 mo; P = 0.0125)	5T4 immune response correlated with longer TTP

clinical trial. The immune response surrogate was established as a linear combination of baseline 5T4-specific antibody titers, hemoglobin level, and hematocrit, which were the only variables to remain statistically associated with survival after adjustment for standard of care. The availability of a predictive surrogate for therapeutic responses could enable better patient selection for vaccine treatment. These data need further prospective validation.

### MVA-5T4 clinical data in CRPC

TroVax<sup>®</sup> has been evaluated in an open-label Phase II trial in metastatic CRPC patients in which the vaccine was administered either alone or in combination with GM-CSF.<sup>57</sup> The 27 patients evaluated all had progression by PSA, RECIST, or bone scan criteria, despite prior ADT and taxane therapy. Patients with a low performance status or autoimmune disease were excluded. Fourteen patients received TroVax<sup>®</sup> alone, and 13 patients received TroVax<sup>®</sup> and 12 cycles of GM-CSF. The study was primarily designed to monitor safety and both antibody and cellular immunologic endpoints. In addition, serum PSA, computed tomography (CT), and bone scan progression were measured. There were no grade 3 or 4 toxicities in either arm of the trial. The most common adverse event reported was injection site irritation. Of the 24 patients evaluable for measurement of immune response, all had anti-5T4 antibody responses, and nine of 24 had a positive 5T4 ELISPOT assay response, without significant differences between the study arms.<sup>57</sup> Overall, 15 of 27 patients had a period of PSA stabilization. Six patients had a decreased PSA velocity, and five patients in the TroVax<sup>®</sup> and GM-CSF arm had a transient 4-week decrease in PSA of 30% or more that was attributed to the GM-CSF, as no patients in the TroVax<sup>®</sup> alone arm had a PSA decline.<sup>57</sup> There were no objective responses based on CT or bone scans in either treatment arm. Interestingly, patients in the TroVax<sup>®</sup> alone arm had an increased time to progression (TTP) compared with the TroVax<sup>®</sup> and GM-CSF arm (4.05 months vs 2.1 months, P = 0.0125), which did reach statistical significance. This trend clearly needs to be explored further in larger studies.

At the time of publication, this trial had not met its median survival endpoint; however, a preliminary retrospective analysis was performed to correlate immunologic response with clinical progression. Patients with a positive 5T4 cellular response were found to have a significantly increased median TTP (5.6 months vs 2.3 months, P = 0.024) compared with patients who did not.<sup>57</sup>

Although a Phase II trial evaluating TroVax<sup>®</sup> and docetaxel versus docetaxel alone for CRPC was terminated by its sponsor,<sup>58</sup> a similar study began accrual in September 2010.<sup>59</sup> This trial, NCT01194960, was designed to evaluate the addition of TroVax<sup>®</sup> to 10 cycles of docetaxel on progression-free survival by RECIST and PCWG2 criteria at week 37. Eligible patients will have demonstrable metastatic disease, will not have had prior chemotherapy, and will remain on ADT to keep serum testosterone under 50 ng/dL. The estimated final data collection date of this study is expected to be mid-2012.

## MVA-5T4 for CRPC: future directions

TroVax<sup>®</sup> has now been widely evaluated in cancer patients with a variety of different cancers and in combination with several other agents. These studies have confirmed that vaccination is generally safe and feasible in patients with advanced cancers. To date, the evidence suggests that those patients who develop an immune response after vaccination, particularly a 5T4-specific antibody response, also exhibit improved therapeutic responses. Recent data in RCC showed that there was a correlation between several host factors (ie, hemoglobin level, hematocrit, and 5T4-specific antibody titers) and clinical response; this needs further validation in prospective trials and in other tumors.<sup>56</sup>

The use of TroVax<sup>®</sup> in combination with other therapies will also be important to further validate in larger series. There is increasing evidence that cytotoxic chemotherapy, radiation therapy, and possibly targeted therapy result in the release of tumor-associated antigens and can elicit an immune response. The addition of vaccines to patients with such antigen release may provide an additive and/or synergistic approach to improve therapeutic responses to other therapeutic modalities. The optimal schedule, dosing, timing, and methods for monitoring responses are all areas that will need to be better evaluated and defined. Recent data from studies of ipilimumab have suggested that the kinetics of antitumor immunity may be very slow and missed by more standard RECIST criteria. This may be overcome by evaluating survival endpoints or using modified response criteria, such as the recently described immune response criteria, in which patients without clinically significant disease progression continue on immunotherapy until a definitive response is seen or clinically meaningful progression occurs.<sup>60</sup>

Although the clinical use of TroVax<sup>®</sup> for CRPC currently consists of a small number of patients, the preliminary data regarding safety and immunologic responses are in

line with those from the CRC and RCC literature. Due to the rather modest objective clinical responses of tumor vaccines, they are increasingly utilized as a component of combination therapy. The current Phase II trial for CRPC is following this trend by combining TroVax<sup>®</sup> with the current first-line therapy, docetaxel. These data are needed to further establish the safety and potential efficacy of the vaccine, which will need to be validated in a larger and prospective Phase III trial. In addition, the vaccine should be tested in combination with other agents demonstrating activity in CRPC, such as cabazitaxel and abiraterone, and other potential vaccine adjuvants, such as ipilimumab.

The selection of predictive biomarkers would be a major advance in the field and could help select the most appropriate patients for inclusion in vaccine clinical trials. A larger number of patients with CRPC will allow such analyses to be performed. Future studies should include collection of prostate biopsy tissue, urine, and/or serum, when feasible, to assess various biomarkers that identify subgroups of patients that may benefit more from TroVax<sup>®</sup>.<sup>55,60</sup> Potential biomarkers might include simple host factors as reported in RCC patients, serum markers (eg, cytokine, chemokines, vascular endothelial growth factor), immune gene polymorphisms, and single gene and genome-wide mutation analyses.

The modest therapeutic responses seen with current vaccines and other immunotherapeutic agents have shed light on the potential clinical benefit with immunotherapy. CRPC represents a logical tumor on which to focus, because vaccines have already shown promise for the disease, 5T4 expression is common, and vaccination is safe, has limited impact on quality of life, and may be combined with other regimens commonly employed in CRPC treatment, such as chemotherapy, radiation therapy, and hormone treatment. The future will depend on establishing well-designed clinical trials that incorporate more appropriate response criteria and correlative laboratory and immune response assays.

## Disclosure

The authors report no conflicts of interest in this work.

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