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Therapeutic vaccines in metastatic castration-resistant prostate cancer: principles in clinical trial design

Ravi A Madan, MD[1], **Mahsa Mohebtash, MD**[2], **Jeffrey Schlom, PhD**[3], and **James L Gulley, PhD MD FACP**[†,4]

[1]Associate Clinical Investigator, Laboratory of Tumor Immunology and Biology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, 10 Center Drive, Room 8B09, Bethesda, MD 20892, USA

[2]Clinical Fellow, Laboratory of Tumor Immunology and Biology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, 10 Center Drive, Room 8B09, Bethesda, MD 20892, USA

[3]Chief, Laboratory of Tumor Immunology and Biology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, 10 Center Drive, Room 8B09, Bethesda, MD 20892, USA

[4]Senior Clinician, Director, Clinical Trials Group, Laboratory of Tumor Immunology and Biology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA

Abstract

Although docetaxel was approved for the treatment of metastatic castration-resistant prostate cancer in 2004, additional therapies are still required. Prostate cancer is often slow-growing and expresses many tumor-associated antigens, making it a feasible target for immunotherapy. Several therapeutic cancer vaccines have been developed for prostate cancer, including antigen-presenting-cell-based, vector-based, and whole tumor cell vaccines. Initial trials demonstrated that vaccine approaches have limited toxicity. Clinical trials of targeted biologic therapies have demonstrated that patient selection is vital, and there is preliminary evidence that clinical parameters can be used to encompass metastatic prostate cancer patients who will more probably respond to vaccine treatment. In addition to appropriate patient selection, a successful clinical trial must have an appropriate primary endpoint as well. Three randomized, 'placebo'-controlled studies in metastatic castration-resistant prostate cancer have suggested a clinically significant survival advantage in spite of a lack of improvement in time to progression, implying that overall survival is the ideal endpoint for such trials. Careful examination of data from completed immunotherapy clinical trials in prostate cancer has identified appropriate patient populations and endpoints. Those principles need to be applied to future trial design to properly evaluate prostate cancer vaccines.

[†] Author for correspondence Clinical Trials Group, Laboratory of Tumor Immunology and Biology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA, Tel: +1 301 435 2956; Fax: +1 301 480 5094; gulleyj@mail.nih.gov.

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Keywords

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1. Rationale for vaccines in the treatment of prostate cancer

As a consequence of prostate-specific antigen (PSA) screening and digital rectal exam, prostate cancer patients can often be cured at diagnosis by surgery or radiation therapy. Unfortunately, 20% to 40% of patients may still have disease recurrence, regardless of the type of primary intervention [1–4]. When prostate cancer recurs after initial definitive therapy, sequential hormonal manipulations are often employed until metastatic disease develops [5]. In 2004, docetaxel became the first FDA-approved chemotherapeutic agent for metastatic castration-resistant prostate cancer (CRPC), resulting in an overall survival benefit of 2.4 months [6,7]. Since then, no additional agents have been approved for the treatment of metastatic CRPC. However, several therapeutic cancer vaccines have been investigated in both early-and late-stage disease, with intriguing results.

From a clinical perspective, several aspects of prostate cancer make it an ideal target for immune-based therapies. Prostate cancer is an indolent disease, potentially allowing time for an activated immune system to mount an effective response [8]. Serum PSA levels allow for the detection of minimal disease before it is detectable on imaging studies, which may be an ideal setting for immune-based treatments [5]. In addition, the prostate is a nonessential organ, and targeting tumor-associated antigens (TAAs) specific to prostatic tissue is unlikely to have a significant negative clinical effect.

From an immunological standpoint, prostate cancer cells produce several gene products that are suitable targets for immunotherapy [9,10]. Although these TAAs can be recognized by cytolytic T cells, in many patients the level of T-cell response is insufficient to generate an effective antitumor response. However, therapeutic cancer vaccines can augment the immune response via several strategies to enhance immune stimulation [11].

Several TAAs are both unique to and/or overexpressed in prostate cancer cells. PSA is a 34-kDa protein with expression confined to prostate cancer cells and the epithelial cells within the prostate, making it a target for many prostate cancer vaccines [12,13]. Prostate-specific membrane antigen (PSMA) is a 100-kDa transmembrane glycoprotein that is expressed in both primary and metastatic prostate cancer cells [14]. Androgen deprivation, which is the primary therapy for metastatic prostate cancer, augments PSMA expression, potentially enhancing its utility as a target for cancer vaccines [15]. Prostatic acid phosphotase (PAP) is another TAA target in prostate cancer. This 102-kDa glycoprotein is overexpressed in prostate cancer cells and may play an important role in disease progression [16,17]. In addition, other prostate antigens such as new gene expressed in prostate (NGEP) and T cell receptor gamma alternate reading frame protein (TARP) have been identified and are currently under investigation as potential future targets of vaccine-mediated therapy [18,19]. Although initial vaccine studies did evaluate humoral responses to TAAs, recent trials have focused more on T-cell-specific immune responses to these antigens as potential markers of vaccine-induced immune response [20].

2. Vaccine strategies

Several therapeutic prostate cancer vaccines have been developed in recent years that employ multiple strategies to generate a targeted immune response. The sipuleucel-T vaccine (Provenge; Dendreon Corporation) represents a patient-specific approach that utilizes *in vitro* stimulation of a patient's own antigen-presenting cells (APCs). Sipuleucel-T is derived from a patient's own peripheral blood mononuclear cells, which are collected through leukapheresis and exposed to PA2024 *in vitro* for 48 hours. PA2024 is a recombinant fusion protein of the TAA human PAP and GM-CSF, which enhances APC activation and maturation. After the patient's peripheral blood cells are treated *in vitro*, they are processed and then this APC-enriched product is reinfused into the patient in an attempt to trigger a focused immune response against prostate cancer cells [21,22].

Vector-based vaccines such as PSA-TRICOM (Prostvac) were developed by the National Cancer Institute (NCI) as part of a Collaborative Research and Development Agreement with Therion Biologics, and subsequently licensed to BN Immunotherapeutics. Prostvac is a vector-based vaccine platform consisting of a prime vaccination with a recombinant vaccinia-based vaccine followed by multiple booster vaccinations with a replication-defective fowlpox-based vaccine. Each vaccine vector contains the transgenes for PSA and three human T-cell costimulatory molecules (TRICOM) to enhance T-cell activation. The PSA transgene has been modified to enhance T-cell response [23–26]. Upon subcutaneous injection, Prostvac is able to deliver these transgenes *in situ*, where they are processed by the patients' own APCs in their skin and then expressed on the cell surface, leading to T-cell activation.

Poxviruses have many advantages as a vector for cancer vaccines. First and foremost, they are relatively safe and have been used in over 1 billion humans to prevent smallpox for over 200 years. In addition, all viral genes are processed with viral enzymes in the host's cellular cytoplasm, so there is no risk of integration within the host DNA. The poxviral genome is large enough for the transfer of multiple transgenes, including TAAs and costimulatory molecules [27,28]. By including costimulatory molecules as part of the vaccine construct, APC function is enhanced [27,29–31]. Once injected subcutaneously, the viral proteins generate an inflammatory response, resulting in the trafficking of immune cells, including APCs, to the vaccination site. Poxviruses also have high rates of cellular infectivity, so it is highly likely that a significant number of APCs will be infected [27].

Vaccines consisting of whole tumor cells are also patient-nonspecific and have been designed to create a targeted immune response. GVAX (Cell Genesys Inc.) is an allogeneic cellular immunotherapy consisting of two irradiated cell lines derived from metastatic prostate cancer (LNCaP and PC-3). These cell lines are transfected with a gene to secrete GM-CSF, which serves as an immune adjuvant. When the vaccine is injected, GM-CSF is thought to help traffic APCs to the site and augment their activation and maturation in response to tumor cells. The APCs then process the TAAs from the cell lines in the vaccine and subsequently induce an immune response [32]. In spite of encouraging preliminary trial results for GVAX, recent negative trial outcomes have curtailed its clinical development

[33,34]. However, as will be discussed below, the clinical results with this vaccine may have been more promising if a more appropriate patient population had been evaluated.

3. Appropriate patient selection in prostate cancer vaccine trials

Although prostate cancer has multiple unique antigens, there is no known parameter (such as Her-2 overexpression in breast cancer) that can be used as an identifier of likely responders to vaccine-based therapy. Generally speaking, the larger trials involving prostate cancer vaccines enroll a variety of patients with all forms of the disease, including those who are least likely to respond to an immune-based therapy.

In identifying the ideal population for a cancer vaccine trial, one should try to define which patients are most likely to respond to a cancer vaccine. Since these treatments rely on immune activation, patients with rapidly progressing disease may not have enough time for a vaccine to affect the immune system. Previous chemotherapy treatments may also affect the potential benefit of a vaccine. In trials evaluating a vaccine targeting carcinoembryonic antigen, the more recently patients had been treated with chemotherapy, the less likely they were to have an antigen-specific T-cell response ($p = 0.005$). Patients who had been treated with more numerous chemotherapeutic regimens were also less likely to have an immune response ($p = 0.032$) [35]. Finally, patients with large tumor volume may also be less likely to respond to cancer vaccines. Based on animal and human models, there is a proportional increase in the number of regulatory T cells (Tregs) with greater tumor burden [36,37]. This is significant because Tregs can diminish the effects of cancer vaccines on T cells by limiting T-cell expansion and activation [38,39]. In addition, bulky tumors have been shown to produce TGF-β, IL-10 and indolamine-2,3-dioxygenase, which can also inhibit T-cell activation [40,41]. Based on these findings, the ideal patient for a cancer vaccine would have slow-growing, and/or low-volume disease and minimal prior exposure to chemotherapy.

Such patients may be easier to identify in the earlier stages of disease than in metastatic CRPC. In early-stage disease, Gleason score may more accurately reflect the tumor's aggressiveness, and PSA may reflect the volume of disease. In fact, a small Phase II trial at the NCI demonstrated the potential benefits of a vaccine in such a population. In a trial that randomized nonmetastatic CRPC patients to either an earlier form of a poxviral vector-based vaccine targeting PSA (rV-PSA + rV-B7.1 prime, rF-PSA boost) versus an FDA-approved second-line hormonal agent (nilutamide), a survival analysis indicated that patients randomized to receive initial treatment with vaccine had improved overall survival. Furthermore, patients randomized to initial treatment with vaccine who had a Gleason score < 7 or PSA < 20 appeared to have an even larger survival advantage over patients initially treated with nilutamide [42]. These data suggest that less aggressive, relatively low-volume disease is more responsive to an activated immune response. Although a trial involving the sipuleucel-T vaccine in metastatic CRPC patients showed a trend toward a survival benefit in patients with a Gleason score of ≤ 7, it is likely that in the metastatic setting, Gleason score is a less dominant factor, and other factors may be required to characterize the disease state of likely responders [43].

Although previous trials suggest that minimal tumor volume may portend a greater clinical benefit from vaccine, metastatic CRPC remains the most practical population to study therapeutic cancer vaccines [44]. For patients with a rising PSA after initial therapy and no evidence of disease on scans, prognosis is highly variable, with many patients surviving more than a decade [45,46]. Therefore, without clear guidelines on assessing progression after vaccine therapy in these populations, analyzing clinical benefit with vaccines is difficult. Currently, smaller trials are evaluating vaccines in combination with hormonal agents in these populations in order to determine clinical benefit and potential endpoints for future trials [42,47].

Since metastatic CRPC patients represent perhaps the best population to evaluate clinical endpoints in patients treated with therapeutic vaccines, a method to enrich trials with patients who are likely to respond to vaccine treatment is desirable. In this regard, nomograms may be helpful. One in particular, the Halabi nomogram [48], has shown potential in patient selection for vaccine trials. The Halabi nomogram is derived from an analysis of 1101 patients with metastatic CRPC who were treated with chemotherapy or second-line hormonal therapy in Cancer and Leukemia Group B studies between 1991 and 2001. The nomogram utilizes seven base-line parameters that were found to be significant, based on evaluation of these patients. In addition to Gleason score, a patient's performance status, PSA, alkaline phosphatase, lactate dehydrogenase, hemoglobin and the presence of visceral disease are incorporated into the nomogram [48].

Although the nomogram was initially developed to predict survival in patients treated with chemotherapy or second-line hormonal therapy and to assist in stratifying patients for clinical trials, it may also be of benefit in selecting patients who are likely to respond to vaccine-mediated therapies. The broader assessment of markers for both disease volume and aggressiveness may provide a more expansive assessment of patients than a lone variable such as Gleason score or PSA. Based on this premise, the Halabi nomogram was used in the overall survival analysis of a Phase II study at the NCI in which 32 chemotherapy-naïve, metastatic CRPC patients were treated with PSA-TRICOM. The patients were retrospectively placed into two groups based on a predicted survival of ≥ 18 months compared to < 18 months. Patients with a predicted survival of ≥ 18 months had features consistent with smaller tumor volume and more indolent disease based on the Halabi nomogram. For patients with a predicted survival of < 18 months, there was only a modest 2.3-month improvement after treatment with PSA-TRICOM (median 14.6 versus 12.3 months) over that predicted. For patients with a predicted survival of ≥ 18 months, there was a more pronounced improvement after treatment with PSA-TRICOM relative to the predicted survival. The predicted survival of the group with better prognostic features was 20.9 months compared to an actual survival that will meet or exceed 37.3 months—an improvement of > 16 months. In spite of the small size of this study, these results suggest that metastatic CRPC patients with more indolent disease characteristics who are treated with vaccine may have an overall survival better than predicted with chemotherapy or second-line hormone therapy [44]. Perhaps most important, these data suggest that a nomogram that is routinely used to evaluate multiple disease characteristics could be used to select a group of patients (in this case patients with a predicted survival of ≥ 18 months) who would probably respond to vaccine treatment. Future prospective trials could focus on such a

population to determine the efficacy of a vaccine. Indeed such studies are currently being designed to further test this hypothesis.

Similarly, in the sipuleucel-T trial demonstrating enhanced patient survival, patients had relatively good baseline characteristics (no visceral disease, Eastern Co-operative Oncology Group (ECOG) score 0 to 1) and their median PSA, LDH, alkaline phosphatase and hemoglobin reflected a relatively good prognosis [49]. The only presented Halabi score parameter used to group patients in this trial was Gleason score. Interestingly, although there were improvements among vaccinated patients in all subgroups, differences in both survival and time to progression were substantially larger in the Gleason ≤ 7 subgroup. In addition, early data suggested that immune responses were significantly improved in this subset [50].

Recently presented data suggest that the overall survival of asymptomatic, metastatic CRPC patients treated with GVAX was similar to those patients treated with docetaxel in a randomized Phase III study (HR 1.01). Notably, however, in the subgroup of patients with a Halabi nomogram predicted survival of > 18 months, there was a trend toward improved survival in patients randomized to treatment with vaccine compared with patients treated with docetaxel (HR 0.9) [51].

Finally, a positive vaccine trial in another disease supports the use of vaccine earlier in disease. A Phase III follicular lymphoma trial employing a patient-specific autologous, tumor-derived idiotype vaccine treatment demonstrated an improvement in time to disease recurrence ($p = 0.045$) [52]. This trial only enrolled patients who had complete responses to previous therapy whereas two previously reported studies of idiotype vaccines, that did not meet their endpoints, allowed patients to enroll with measurable disease. It is possible that the greater amount of disease in the two earlier studies prevented the vaccine treatment from demonstrating a clinical benefit, which was seen in the third trial.

4. Overall survival as an endpoint

When designing a clinical trial, the selection of an appropriate primary endpoint may well be as important as the selection of an appropriate patient population. Although for many agents the path to approval is paved by objective response rates in clinical trials, metastatic CRPC is less likely to yield measurable changes in disease volume in response to treatment. In fact, only 12% to 17% of patients in the trials that led to FDA approval of docetaxel in metastatic CRPC had responses to treatment, due in large part to the fact that about 50% to 60% of patients have metastasis only to bone, which is best evaluated by whole-body scintigraphy [6,7]. Complete responses with whole-body scintigraphy are rare. In addition, there are no broadly accepted criteria to assess partial responses for whole-body scintigraphy. Response Evaluation Criteria in Solid Tumors (RECIST) are often employed in clinical trials where clinical benefit is evaluated by reduction in tumor size (soft tissue only), but in light of the low response rate of metastatic CRPC even to chemotherapy, the value of RECIST may also be limited in vaccine trials in this cancer [53,54]. Furthermore, an immune response may cause transient increases in the size of lymph nodes, which could be misconstrued as progressive disease [55–57].

Evaluating clinical benefit is further complicated in vaccine trials in metastatic CRPC, where an overall survival benefit can be seen even though there is no improvement in time to progression (Table 1). A randomized Phase II study of the vector-based vaccine PSA-TRICOM provides a good example. In an industry-sponsored trial, 125 patients with metastatic CRPC and Gleason scores ≤ 7 were treated with PSA-TRI-COM (ratio 2:1) or an empty fowlpox vector as control. Patients randomized to the vaccine arm were treated with an initial dose of vaccinia-based PSA-TRICOM and monthly boosts of fowlpox-based PSA-TRICOM, while control patients were given monthly subcutaneous injections of fowlpox. The primary endpoint of this study was time to progression, determined by new or enlarging soft tissue or bone metastasis. The study did not meet its primary endpoint, but a survival analysis indicated a clear clinical benefit [58]. The median overall survival was 8.5 months longer in the vaccine arm compared with the control arm ($p = 0.016$), suggesting that in spite of a lack of improved time to progression, there was a long-term survival advantage for patients treated with PSA-TRICOM [59].

A Phase III, placebo-controlled trial in patients with metastatic CRPC randomized 2:1 in favor of the sipuleucel-T vaccine showed similar results. The vaccine was administered on weeks 0, 2 and 4, and patients were allowed to cross over after 8 weeks if there was clinical progression (new lesions on imaging or increased pain) [49,60]. The trial enrolled 82 patients in the treatment arm and 45 patients in the placebo arm. Thirty-four patients on placebo went on to receive sipuleucel-T as part of the crossover component. The trial failed to meet its primary endpoint of time to progression, although progression favored patients randomized to the sipuleucel-T arm (16.6 weeks versus 10 weeks; $p = 0.052$). In spite of the crossover design and failure to reach the primary endpoint, overall survival improved by 4.5 months in patients randomized to treatment with vaccine (25.9 months versus 21.4 months; $p = 0.01$). This disparity in overall survival increased at 36 months, with an estimated survival of 34% for the sipuleucel-T arm versus 11% for the placebo arm ($p = 0.005$) [49]. This led to a larger, definitive, overall survival endpoint, randomized, placebo-controlled Phase III study. This study again showed no time to progression benefit relative to placebo, but did demonstrate a survival advantage. The median survival for the 341 patients who received vaccine was 25.8 months compared with 21.7 months for 171 patients treated with placebo. The vaccine was well tolerated and will probably be submitted to the FDA by the end of 2009 for approval in the treatment of metastatic CRPC [61].

Although the concept that a therapeutic agent could increase survival without changing time to progression may initially seem implausible, it is likely that vaccine-mediated therapies induce a dynamic immune response that can persist and may act in combination with subsequent thereapies to improve clinical outcomes. There are emerging preclinical and clinical data to support this concept. Murine studies indicate that vaccine combined with docetaxel has a greater antitumor effect than either agent alone and that vaccine followed sequentially by docetaxel generates the greatest vaccine-induced immune response [62]. It has been noted in several clinical trials involving vaccines that patients treated with vaccines have had better than expected responses to subsequent chemotherapy [55,63,64]. One specific example involves metastatic CRPC patients treated with either the sipuleucel-T vaccine or placebo. These patients were then evaluated for overall survival after treatment with docetaxel. For the 51 patients treated with vaccine followed by chemotherapy, overall

survival was 34.5 months compared with 25.4 in 31 patients who were treated with placebo followed by chemotherapy (p = 0.023) [65]. These data suggest that chemotherapy may be able to take advantage of a smoldering immune response, resulting in improved clinical outcomes; however, prospective randomized trials are required to confirm this hypothesis.

5. Expert opinion

5.1. Lessons learned from GVAX

In spite of promising early data from trials involving the allogeneic whole tumor cell vaccine GVAX, including improvements in overall survival compared with predicted survival in Phase II studies, two Phase III trials investigating this particular platform ended abruptly in 2008 [66,67]. Vaccine immunotherapy with allogeneic prostate cancer cell lines (VITAL)-2 was designed to compare docetaxel and prednisone versus docetaxel and GVAX in patients with symptomatic, metastatic CRPC. The trial was discontinued in August 2008 when an interval data review indicated 67 deaths in the combination arm versus 47 deaths in the docetaxel-alone arm. A subsequent review of the data did not suggest that the vaccine itself conveyed any additional toxicity; the vast majority of deaths were due to disease progression [68]. Indeed, with further follow-up the differential between the two arms has decreased to 11 deaths (85 versus 76 deaths). Although both arms in VITAL-2 appeared to be well balanced, recruitment of patients with symptomatic disease may explain the relative ineffectiveness of the addition of vaccine to docetaxel. Patients with symptomatic prostate cancer are likely to have more aggressive disease features. In fact, patients who enrolled in VITAL-2 had a Halabi median predicted survival of only 13 months [68]. Therefore, the failure to demonstrate the benefit of GVAX in VITAL-2 may be due to the selection of patients not likely to respond. Indeed, in VITAL-2 only 18% of patients had a Halabi predicted survival of ≥ 18 months. In that select subgroup, GVAX plus docetaxel appeared to do better than docetaxel with prednisone (HR 0.8) [68].

The role of regulatory immune cells should also be considered in evaluating the VITAL-2 trial. These cells serve to moderate the body’s immune response by maintaining a degree of self-tolerance and thereby decreasing autoimmunity, but they may also decrease responsiveness to therapeutic cancer vaccines [38,39,69–71]. Increased tumor volume, which directly correlates with many prognostic variables of the Halabi nomogram, has also been correlated with an increased quantity of regulatory immune cells and poor clinical outcome [36,37,72–75]. In addition, emerging data suggest that the higher levels of GM-CSF secreted by the GVAX vaccine may enhance the suppressive activity and number of regulatory immune cells [76–78]. Thus it is possible that the combination of GM-CSF in a setting of a large volume of regulatory immune cells may have contributed to poor clinical outcomes in VITAL-2. Further analysis of blood specimens of patients enrolled on this trial will be required to fully evaluate this hypothesis, but the possibility serves to highlight the need for appropriate patient selection.

VITAL-1, employing the same autologous whole tumor cell vaccine as VITAL-2, may have also faltered in part because of the selection of patients with more advanced disease than is ideal for vaccine-based monotherapy. In a previous Phase II study of GVAX, for the 22 patients treated at the highest dose of vaccine (subsequently used in the VITAL-1 and 2

studies) the Halabi predicted survival was 22 months compared with an actual overall survival of 35 months [66]. In contrast, the metastatic CRPC patients on VITAL-1 were randomized to GVAX versus docetaxel with prednisone. This possible randomization to chemotherapy may have caused patients to defer treatment on this study and thus have more advanced disease at randomization than those patients in the Phase II study. Of the 621 patients enrolled, only 264 (42%) had Halabi predicted survival of ≥ 18 months. Interestingly, of the patients in VITAL-1 who had a predicted survival of ≥ 18 months, there was a trend toward a survival advantage for those treated with GVAX relative to those treated with docetaxel (10% improvement in overall survival; hazard ratio (HR) 0.90). It is also important to note that only 69% of patients treated on-study with GVAX went on to get docetaxel [51]. This would indicate that about one-third of VITAL-1 patients did not receive chemotherapy, yet the vaccine cohort had a similar survival to the control group who all received chemotherapy. This takes on even further significance when the minimal toxicity seen with GVAX is also taken into account.

In addition, the HR of 1.01 suggested similar overall survival to chemotherapy, but with much fewer side effects (serious adverse events in 16.9 versus 4.2%) [67]. However, as this was not a non-inferiority trial, VITAL-1 was terminated in October 2008 after it was determined that the trial had only a 30% chance of showing an overall survival benefit. However, it is possible that further follow-up may show even more advantage to vaccine. Indeed, only 371 deaths occurred in 621 enrolled patients [51]. As discussed earlier, the survival advantage (demonstrated by the separation of the Kaplan-Meir survival curves) in the randomized Phase II trials of sipuleucel-T vaccine and PSA-TRICOM did not become apparent for almost 12 and 15 months, respectively (Figure 1) [49,58]. Perhaps with longer follow-up, a similar trend will also be seen with the VITAL-1 data, especially in the subgroup with longer predicted survival. Indeed, the apparent separation of the survival curves in VITAL-1 with chemotherapy associated with improved survival in those patients dying earlier and vaccine associated with improved survival after about 18 months further suggests improved survival on immunotherapy of this subset of patients. Finally, it is interesting that the median Halabi predicted survival of the patients treated in the definitive sipuleucel-T study was about 21 months (M. Frohlich, Dendreon Corporation, pers commun). This is similar to the median predicted survival of patients in the better prognostic group in the NCI Phase II PSA-TRICOM study, and further bolsters the argument that patients with less aggressive disease or lower tumor burdens (and therefore longer predicted survivals) comprise the patient populations more likely to show a clinically significant difference in overall survival when treated with vaccine.

5.2 Optimal trial design for vaccines in metastatic CRPC

Investigators should be cognizant of lessons learned from previous clinical experience with vaccines and other biologics. Prudent and strategic trial design allowed the monoclonal antibody trastuzumab (Herceptin; Genentech Inc.) to demonstrate efficacy. Since trastuzumab is only effective in 20% to 30% of all breast cancer patients, had the initial trials (which showed a modest benefit) been done in all breast cancer patients, it is likely that the response rate would have been only a fraction of the 18% seen [79,80]. Once there was some evidence of success, less heavily pre-treated patients were then evaluated, leading to nearly a

doubling in response rate. When combined with chemotherapy, the agent was ultimately approved by the FDA [81,82].

Unfortunately, in prostate cancer there is no single marker that is the equivalent of Her-2 as both a target and an identifier of likely responders, so alternative selection methods must be developed. As selection criteria, both PSA and Gleason score have limitations; PSA is too variable from patient to patient, and Gleason score may be a decade removed from the development of metastatic disease. Nomograms appear to be more valuable in that they often incorporate several parameters important to disease kinetics. Although there are no specific nomograms developed to predict response to vaccine therapy, existing nomograms may assist in selecting appropriate patients for vaccine clinical trials. One such nomogram that has shown some preliminary value is the Halabi nomogram. In a Phase II vaccine study, metastatic CRPC patients with characteristics consistent with more indolent disease had a better survival outcome than those with worse prognostic features [42,48]. Perhaps with a broader vaccine experience in the future, patient selection criteria specific to vaccine therapy can be developed. While enrollment of a selected population is no guarantee of success, it will provide the best opportunity for vaccines to demonstrate clinical benefit. If these preliminary trials are successful, other strategies could be developed to broaden the scope of utility to more patients.

The primary endpoint of a trial is also crucial to its success. With metastatic CRPC trials using effective cytotoxic chemotherapy demonstrating objective response rates of ≤ 17%, it is unreasonable to use RECIST as primary evaluation criteria for treatment with vaccine [6,7]. As has been demonstrated in two vaccine trials using different platforms, even time to progression may be misleading as an endpoint in immunotherapy trials [49,59]. Unlike cytotoxic agents, which have their greatest effect soon after administration, vaccines likely initiate a dynamic immune response that increases over time, perhaps allowing for initial progression followed by subsequent response or stabilization [73]. Therefore, in metastatic CRPC vaccine trials, overall survival should be the primary endpoint.

Another factor in successful clinical trial design is subsequent therapies. In the setting of a dynamic immune response potentially established by vaccines, subsequent treatments may be more effective, further emphasizing the need to use overall survival as endpoint [73]. Patients may initially progress on vaccine therapy, then do surprisingly well on subsequent therapy [63–65]. It is unclear whether this secondary response is due to the cytotoxic therapy depleting Tregs that could be hindering an immune response, or that an immune response is enhancing the effect of the additional hormonal therapy or chemotherapy. Nonetheless, if possible, therapy subsequent to a vaccine trial should be controlled for as part of the trial.

Metastatic CRPC represents a unique opportunity to test this hypothesis, since there is currently only one approved chemotherapy, docetaxel, shown to affect survival. Add to that the fact that chemotherapy-naïve patients may be the best patient population, and the recommendations for the outline of an ‘ideal’ trial design become clear (Figure 2) [35]. First, chemotherapy-naïve metastatic CRPC patients with indolent disease characteristics should be randomized to either standard docetaxel or vaccine. Upon progression in the vaccine arm or after a set number of doses to establish an immune response, patients on the

vaccine arm would then be treated with a standard docetaxel regimen as well. Since there is no approved second-line agent for metastatic CRPC, subsequent chemotherapies after docetaxel probably do not significantly alter the disease course, but patients must be followed in order to determine the primary endpoint of overall survival. In this trial design, vaccines would have the greatest opportunity for success. Based on previous experience, heavily pretreated patients and patients with very aggressive disease characteristics should not be enrolled on vaccine-based studies, given the low likelihood that they will derive benefit from a vaccine-containing regimen.

Much has been learned about the treatment of metastatic CRPC with therapeutic vaccines. All of that progress is for naught, however, if future trials are not strategically designed. In light of recent clinical trial results, it is likely that upcoming trials will primarily be conducted with APC-based or vector-based vaccine strategies. Enriching patient populations for those most likely to respond by selecting patients with indolent disease characteristics, using overall survival as an endpoint, and controlling for subsequent treatments may not guarantee therapeutic success for vaccine-mediated therapy, but does represent the most prudent approach to future trial design.

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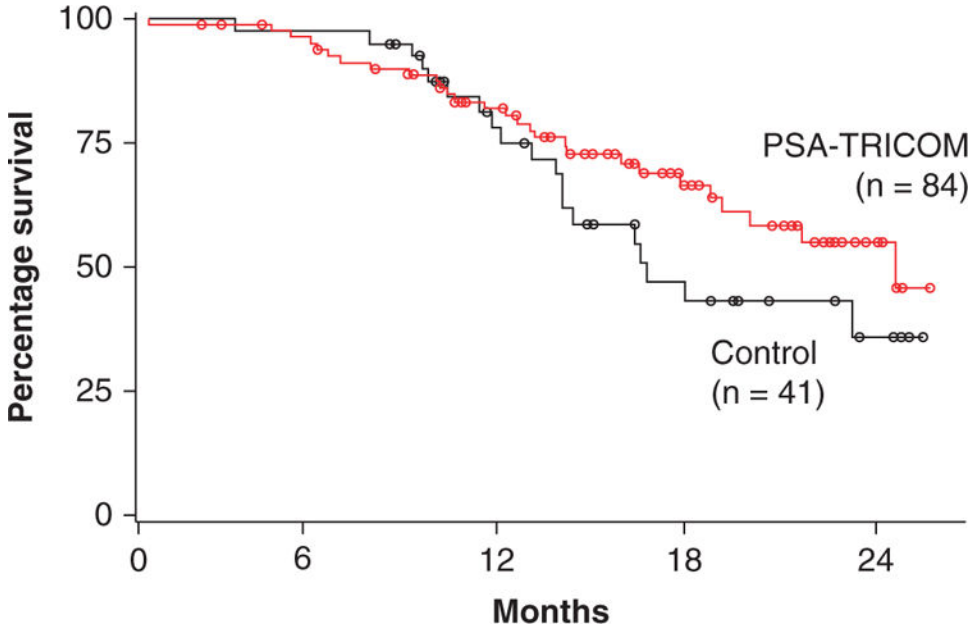

Figure 1.

Overall survival in patients treated with PSA-TRI-COM is better than for those patients treated with placebo vaccine (wild type vector). Adapted from [73] with permission.

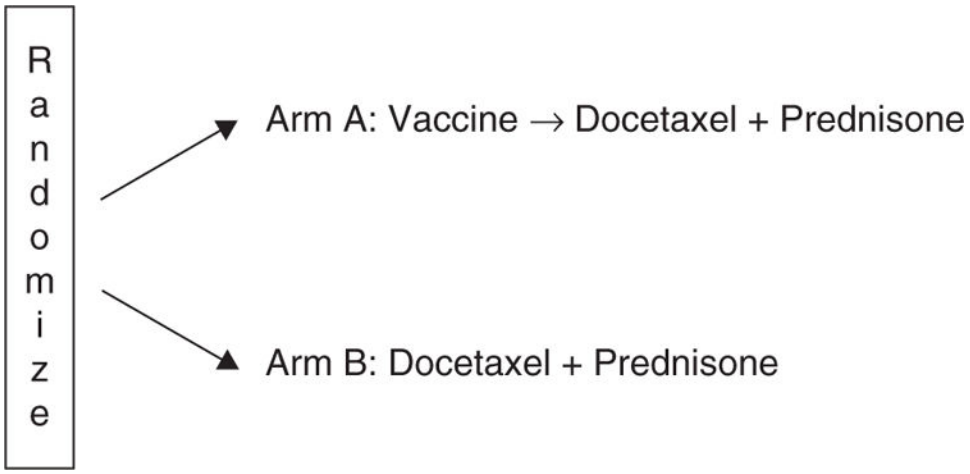

Figure 2.

Proposed design for a planned cooperative group randomized controlled vaccine trial in patients with metastatic castration-resistant prostate cancer who have a >18 month predicted survival by the Halabi nomogram. The primary endpoint is overall survival.

Table 1.

Vaccine trials showing an overall survival advantage despite a lack of time to progression benefit.

Vaccine	n	Results	Ref.
Sipuleucel-T	127 (randomized 2:1)	The median OS favored vaccine (25.9 versus 21.4 months (p = 0.01)). At 36 months estimated OS was 34.1% for vaccine and 11% for placebo (p = 0.005)	[49]
Sipuleucel-T	512 (randomized 2:1)	The median OS was 4.1 months longer for mCRPC patients treated with vaccine compared with placebo (25.8 versus 21.7 months)	[61]
PSA-TRICOM	125 (randomized 2:1)	The median OS was 24.5 months for mCRPC patients treated with vaccine compared with 16.0 months for patients treated with an empty poxviral vector as a control arm (p = 0.016)	[59]

mCRPC: Metastatic castration-resistant prostate cancer; OS: Overall survival;

TTP: Time to progression.