Building on Sipuleucel-T for Immunologic Treatment of Castration-Resistant Prostate Cancer

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Background: Sipuleucel-T is an autologous cellular immunotherapy approved by the US Food and Drug Administration for the treatment of asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer. Its mechanism of action is based on stimulation of the patient’s own immune system to target prostate cancer. Peripheral blood mononuclear cells, including antigen-presenting cells and T cells, are obtained from patients via leukopheresis and treated ex vivo with PA2024, a fusion protein consisting of prostatic acid phosphatase/granulocyte-macrophage colony-stimulating factor antigen.

Methods: Data relating to the potential pharmacodynamic biomarkers associated with sipuleucel-T activity are reviewed, as well as considerations for patient selection and for sequencing sipuleucel-T with other prostate cancer treatments. Possible directions for future development are also discussed, including treatment of less advanced prostate cancer populations, combination treatment, and immune modulation.

Results: Data from three randomized, double-blind, placebo-controlled phase III clinical trials of sipuleucel-T in patients with metastatic castration-resistant prostate cancer have shown improvement in overall survival vs control. Here, we review its developing role in prostate cancer therapy and future directions for development.

Conclusions: There is potential to build on sipuleucel-T to further advance immunotherapy of prostate cancer.

Introduction

Although mortality from prostate cancer is declining within the United States, the rate remains high, with an estimated 28,170 deaths occurring in 2012.1 Localized therapies for newly diagnosed prostate cancer have been successful in curing upward of 75% of patients, but novel therapies for advanced prostate cancer are needed to reduce prostate cancer mortality.
Sipuleucel-T was approved by the US Food and Drug Administration (FDA) in 2010 for asymptomatic and minimally symptomatic patients with metastatic castration-resistant prostate cancer (CRPC). Since then, a number of other treatments have been approved for metastatic CRPC. In 2010 and 2011, both abiraterone acetate and cabazitaxel were approved by the FDA for therapy after prior docetaxel treatment, and denosumab was approved for the prevention of skeletal-related events in patients with bone metastases. More recently, an overall survival (OS) benefit was shown with both radium-223 and enzalutamide in metastatic CRPC, and the latter was approved in 2012. Phase III trials of cabozantinib were initiated after phase II results showed evidence of antitumor activity. Other promising immunotherapies in late-phase development for prostate cancer include prostate-specific antigen (PSA)-TRICOM vaccine (a poxviral-based vaccine directed against PSA) and ipilimumab (an anticytotoxic T-lymphocyte antigen [CTLA-4] monoclonal antibody currently approved for the treatment of metastatic melanoma).

Among these emerging novel therapies, sipuleucel-T is the only immunotherapy with a demonstrated OS benefit for asymptomatic or minimally symptomatic metastatic CRPC. Here, we review the clinical data leading to FDA approval of sipuleucel-T and the practical aspects of treatment. We also discuss potential pharmacodynamic biomarkers associated with sipuleucel-T activity, patient selection and drug-sequencing strategies, and future directions for development.

Sipuleucel-T: Manufacture, Composition, and Mechanism of Action

Sipuleucel-T is unique among marketed anticancer products for its administration and composition: It is an individually tailored treatment manufactured from immune cells specific to each patient. A standard course of sipuleucel-T treatment consists of three doses. Each dose is manufactured from a standard leukapheresis procedure conducted approximately 3 days prior to infusion of the sipuleucel-T dose, from which a patient’s peripheral blood mononuclear cells (PBMCs) are isolated. Those cells, including antigen-presenting cells (APCs), are then cultured ex vivo with PA2024, a fusion protein consisting of prostate acid phosphatase (PAP, a protein present on the majority of prostate cancers) linked to granulocyte-macrophage colony-stimulating factor (GM-CSF). PAP is an ideal antigen for targeting prostate cancer because of its tissue specificity — expression of this protein is primarily restricted to prostate tissue — and the rationale for using PA2024 stems from preclinical data showing that a similar fusion protein was effective in breaking immunotolerance to the PAP self-antigen and inducing prostateitis in rat models. During a 36- to 44-hour incubation at 37°C, the APCs internalize PA2024, resulting in their activation (as measured by CD54 upregulation) and presentation of antigen in association with the patient’s own particular HLA class 1 and HLA class 2 cell-surface proteins. Following incubation, the now-activated PBMCs are reinfused. In vivo, the activated cells comprising sipuleucel-T are thought to stimulate native CD4+ and CD8+ T cells, stimulating an immune response against prostate cancer cells.

Although sipuleucel-T is often described as a “vaccine,” the integration of ex vivo and in vivo leukocyte activation contrasts with a classic vaccine. In the latter, an antigen, or an adjuvant/antigen combination, is administered directly to the patient. Here, the antigen presentation and expansion of effector cells physically occur entirely within the host. Alternatively, sipuleucel-T can be characterized as an “autologous cellular immunotherapy”; however, this description does not incorporate the significant ex vivo processing of the cells, which provides an environment apart from the presumably immunosuppressive cytokines and cellular milieu existing within a patient with ongoing disease progression.

Sipuleucel-T is a cellular product with proportions of immune cells that vary depending on the original apheresis product. The number of APCs, defined as large cells expressing CD54, must be at least 50 million per infusion dose. In addition to APCs, B and T lymphocytes are also present in the product and are activated ex vivo during the manufacturing process, which can further activate APCs. The relative importance of lymphocytes activated ex vivo vs those activated in vivo following infusion is unknown.

Phase III Trials With Sipuleucel-T: Efficacy and Safety Data

Three randomized, double-blind, placebo-controlled phase III clinical trials of sipuleucel-T in patients with metastatic CRPC have been completed to date. The first two trials, designated D9901 and D9902A, were identical in design. Patients with asymptomatic metastatic CRPC were randomized 2:1 to receive sipuleucel-T or control infusions at weeks 0, 2, and 4. In all patients, a standard 1.5–2.0 blood volume leukapheresis was performed approximately 3 days prior to infusion. For the control group, one-third of the leukapheresis product was cultured at 2°C to 8°C without PA2024 and then infused, and the remaining two-thirds was cryopreserved for potential crossover treatment following disease progression. The primary endpoint of both studies was time to disease progression (TTP), and an analysis of OS after all subjects were followed for 36 months or until death was prespecified in both study protocols.

The first study, D9901, included 127 patients and showed a statistically nonsignificant trend toward delayed TTP (hazard rate [HR] for disease progression = 0.69; 95% confidence interval [CI], 0.47–1.01; P = .05). At 36-month follow-up, however, there was a statistically significant 4.5-month prolongation in
median OS with sipuleucel-T (25.9 vs 21.4 months; HR for death = 0.59; 95% CI, 0.39–0.88; \( P = .01 \)).

The second trial, D9902A,\(^{10}\) enrolled 98 patients; the study was discontinued early based on the primary analysis of D9901. This trial demonstrated a similar trend of improved OS with sipuleucel-T, with a median OS of 19.0 vs 15.7 months (HR for death = 0.79; 95% CI, 0.48–1.28; \( P = .33 \)).\(^{10,26}\)

The FDA approval of sipuleucel-T was largely based on the results from the pivotal phase III IMPACT trial (D9902B),\(^{15}\) which included men with asymptomatic or minimally symptomatic metastatic CRPC. Eligibility criteria included demonstrable metastatic disease on bone scan or CT scan, no visceral metastases, no corticosteroid use, and no pain requiring opioid analgesia. The primary endpoint was OS, and the secondary endpoint was time to objective disease progression. Additional endpoints included immune responses, PSA changes, and safety. A total of 512 patients were randomized 2:1 to receive sipuleucel-T (n = 341) or control (n = 171). The primary endpoint was met, with a 22% reduction in the risk of death with sipuleucel-T vs control (HR for death = 0.78; 95% CI, 0.61–0.98; \( P = .03 \)) and a 4.1-month prolongation of median OS (25.8 vs 21.7 months). At 36 months, the probability of survival was 31.7% in the sipuleucel-T group compared with 23.0% in the control group.

Subjects in the control groups of all three trials were allowed to cross over at disease progression to receive treatment with a similar autologous product, APC8015F. This treatment was not randomized and was given at investigator discretion with patient consent. The manufacturing process for APC8015F was identical to that for sipuleucel-T, but APC8015F was produced using the frozen PBMCs obtained from the original leukapheresis rather than a fresh leukapheresis.

For the IMPACT trial,\(^{15}\) 64% of control subjects (n = 109) crossed over to receive APC8015F. The median OS for control subjects who crossed over compared with those who did not was 23.8 months vs 11.6 months. Of note, subjects who received APC8015F had more favorable prognostic features than did those not receiving APC8015F. Subsequent analyses adjusting for prognostic factors around the time of disease progression still revealed a positive treatment effect for APC8015F.\(^{27}\) Thus, it is possible that the true magnitude of OS difference was underestimated in the primary analysis of the phase III trial results.

The safety evaluation of sipuleucel-T included a total of 601 and 303 patients treated with sipuleucel-T and control, respectively, in four randomized phase III studies; three included patients with metastatic CRPC (IMPACT, D9901, and D9902A) and one included patients with androgen-dependent prostate cancer (PROTECT). Adverse events (AEs) reported in >15% of patients who received sipuleucel-T were chills, fatigue, pyrexia, back pain, nausea, arthralgia, and headache. Those reported by ≥5% of subjects with at least twice the frequency in the sipuleucel-T group compared with the control group were chills, pyrexia, headache, myalgia, influenza-like illness, and hyperhidrosis. Most AEs developed ≤1 day following infusion, were mild to moderate (grade 1 to 2), and resolved quickly (within 2 days).\(^{28}\)

The incidence of serious adverse events (SAEs) was comparable between treatment groups: 24% (144 of 601) of patients who received sipuleucel-T and 25.1% (76 of 303) of control patients. There has been no evidence of autoimmune complications following sipuleucel-T treatment. SAEs that occurred within 1 day of infusion were reported in 3.5% (21 of 601) of patients who received sipuleucel-T and 2.6% (8 of 303) of control subjects. SAEs that occurred within 1 day of infusion reported for 2 or more patients who received sipuleucel-T were pyrexia, chills, atrial fibrillation, catheter sepsis, hematuria, hypertension, hypoxia, infusion-related reaction, and nausea.

The incidence of cerebrovascular events was 3.5% in the sipuleucel-T group and 2.6% in the control group. As required by the FDA review team, Dendreon Corp is conducting a phase IV registry design, prospective study (PROCEED, trial NCT01306890)\(^{29}\) to further assess the risk of cerebrovascular events as well as the efficacy and treatment patterns of sipuleucel-T in real-world treatment settings. The PROCEED study is currently enrolling patients.

Potential issues have been raised regarding the sipuleucel-T phase III trials. In particular, it was hypothesized that the observed difference in OS could have been due to a harmful effect of the control intervention in the ≥65-year-old control patients resulting from leukapheresis-induced immunodepletion.\(^{30}\) This hypothesis has been refuted by experts in the field of cancer immunotherapy\(^{31,32}\) and the IMPACT authors.\(^{33}\)

The issue hinges on the assertion that the OS benefit seen in the IMPACT trial was limited to the ≥65-year-old patients. This suggestion is based on the fact that the treatment effect in the IMPACT trial was consistent across all 64 individual subgroups (derived from 27 baseline covariates) assessed,\(^{33}\) with the exception of patients younger than age 65. However, only a small number of control patients (approximately 13%) were <65 years of age, which increased the likelihood for error in this analysis.

Further, in any subgroup analysis, the likelihood of a type-1 error (false-positive result) is considerable, given that one can anticipate approximately one significant result (\( P < .05 \)) by chance alone for every 20 comparisons performed. In fact, independent FDA review concluded that the results were false-positive, attributed to the multiplicity of comparisons.\(^{34}\) Data consistent with this finding include a positive treatment effect in both the older than and younger than age 65 groups in an analysis of the first two phase III trials (D9901 and D9902A) and a consistent treatment effect when the IMPACT trial and the prior phase III trials are dichotomized at the median age in IMPACT of 71 years.\(^{35}\)
No data are available to support the assertion that the control intervention may have had a deleterious effect on patients’ immune systems. The National Institutes of Health experience with serial leukapheresis procedures in more than 400 healthy subjects showed that the decreases in lymphocyte counts after 2 to 9 procedures were not clinically significant, with no increased susceptibility to infectious diseases or cancer. Across the phase III trials, there was no evidence that leukapheresis led to immunodepletion. At 6, 14, and 26 weeks, median white blood cell, absolute neutrophil, lymphocyte, and monocyte counts remained within the normal range in each treatment group. It is important to note that an increased rate of infections would be expected if patients in the placebo group had experienced clinically significant immunosuppression. The incidence of infection-related AEs was similar between the sipuleucel-T and control groups (27.5% vs 27.7%), and the majority (83.9%) of those events were grade 1 to 2. Grade 3 to 5 infections were reported in 5.0% of patients who received sipuleucel-T and in 3.3% of control patients.

**Practical Aspects With Sipuleucel-T**

Production of sipuleucel-T begins at the apheresis center, where patients receive leukapheresis to obtain PBMCs. Although apheresis is a routine procedure at many centers, it must take place at an approved center as part of the licensed product specifications. The unprocessed cells from the leukapheresis are then shipped to one of the three manufacturer’s facilities for product preparation. During the standard processing, the cells are activated through coculturing with the PA2024 fusion protein. The activated cells are then shipped back for infusion, typically at the physician’s own infusion center. This process is repeated three times for a standard course of treatment (Figure) and is coordinated, start to finish, by the Dendreon Corp ON Call Program.

The leukapheresis procedure is generally well tolerated, and premedication is not required. Some side effects that were reported within 1 day of leukapheresis in controlled clinical trials are described in the prescribing information. Both the leukapheresis and subsequent infusion can be safely administered via peripheral venous catheter in most patients. Clinicians should determine whether a central venous catheter (CVC) is required; however, routine placement of CVCs should be avoided. CVCs can be advantageous, as they provide a ready source of

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**Figure.** — Examples of hypothetical entry points (red) for additional treatments to overlap with a standard sipuleucel-T administration (blue). CRPC = castration-resistant prostate cancer, MDSCs = myeloid-derived suppressor cells.
access and reduce the need for repeated peripheral venipunctures. However, they are associated with an increased risk of complications such as infections, occlusions, and thrombosis. Thus, clinicians should carefully weigh the risks and benefits of CVC use on a patient-by-patient basis.

**Potential Pharmacodynamic Biomarkers**

Based on the results of the phase III trials, classic measures of disease progression have not been reliable markers of sipuleucel-T activity, which is consistent with findings from studies of other cancer immunotherapies. This leaves clinicians and patients in need of other pharmacodynamic biomarkers or "clinical feedback" to guide subsequent treatment decisions. A number of potential pharmacodynamic biomarkers have emerged in recent analyses and may prove useful in this regard.

To begin, there is evidence from other trials that sipuleucel-T may prolong PSA doubling time, suggesting that the treatment may alter the disease trajectory. Therefore, it seems likely that such measures of disease kinetics may be useful indicators of sipuleucel-T responsiveness.

Additionally, studies have shown correlations between OS and key parameters measured during the manufacturing process. In an integrated analysis of data from the phase III trials of sipuleucel-T, OS positively correlated ($P < .001$) with the total nucleated cell count and CD54 upregulation (a marker of APC activation). Furthermore, both B-cell activity (humoral response as measured as antibody production) and T-cell activity (measured as titers of cells that produce interferon-$\gamma$ if stimulated with cells presenting the test antigen) were observed with sipuleucel-T treatment in the IMPACT trial. For detectable antibody to PA2024 with a titer > 400 at any point posttreatment, the frequency in the treatment group was 66.2% vs 2.9% in the control group and 28.3% vs 1.4% for PAP. Consonant with this finding was the pattern for T-cell proliferation responses (counting those that were greater than 5-fold at week 6), with a frequency of 73.0% vs 12.1% for PA2024 and 27.3% vs 8.0% for PAP in treatment groups vs control groups. Most important, positive correlations between OS and humoral and T-cell responses were observed. These data support the immunologic mechanism of sipuleucel-T and in the future may provide a potential biomarker for monitoring response to treatment. Other potential biomarkers with sipuleucel-T that have been shown to correlate with OS include eosinophilia and increased serum globulin proteins.

**Patient Selection**

A natural starting point for patient selection is the eligibility criterion for the three phase III trials: asymptomatic or minimally symptomatic men with metastatic CRPC. The strength of the randomized trial is based in part on enrolling a population large enough for population heterogeneities to be well balanced. In the IMPACT trial, 63 individual subgroups were assessed (47 of which were reported by Kantoff et al). There was remarkable consistency of the treatment effect shown across these subgroups, with OS favoring sipuleucel-T in all but the subgroup of patients younger than age 65. As previously noted, the results in this latter subgroup were considered most likely to be false-positive, and the discrepancy between age groups was not seen in analyses from the other phase III trials or when dichotomized by the median age of 71 years.

However, as with any new therapy, further investigation as to benefit in specific subpopulations may be warranted, using the results of the large randomized study as a basis. Thus, whether by conventional clinical features (such as Gleason score or extent of cancer-related pain), established histologic features, novel tests on patients’ tumors (looking for expression of particular proteins), or patients’ blood (eg, addressing the emerging circulating tumor cell quantitation technology), there appear to be opportunities to define a population for which sipuleucel-T would be most beneficial.

Other patient attributes/trial inclusion criteria could potentially be applied more or less strictly (Figure). Examples include patients who have experienced significant symptoms of cancer pain but for whom there is good pain control, perhaps with the use of irradiation of the symptomatic areas. From an immunologic basis, irradiating some of the tumor could favor provision of cancer antigens and immunologic stimulation.

The point in the disease course should be a key consideration for determining whether sipuleucel-T is appropriate. The phase III trials were restricted to asymptomatic or minimally symptomatic disease to enroll patients who were not thought to require urgent treatment with chemotherapy and who would survive long enough to derive benefit from immunotherapy. As highlighted previously, there is a discordance between traditional measures of disease progression (eg, TTP, objective and PSA responses) and OS, and similar findings have been shown in trials of other immunotherapies, suggesting that such a discordance may be characteristic of immunotherapies.

It has been proposed that this discrepancy reflects the time required to mount an immune response following sipuleucel-T treatment. Indeed, the OS curves from the IMPACT trial separated after 6 months, and a recent post hoc analysis of time to disease-related pain showed a similar delay. Thus, the asymptomatic patient with newly diagnosed metastatic disease is clearly an appropriate candidate for sipuleucel-T therapy. Nonetheless, data from the phase III studies showed that the benefit of sipuleucel-T treatment was consistent for patients with asymptomatic and minimally symptomatic disease, suggesting that those with minimally symptomatic disease may also...
be candidates for sipuleucel-T. It should be noted, however, that there are potential costs to deferring treatment: The disease could progress quickly, resulting in the attenuation of host features necessary for mediating an immune response due to either side effects of additional required therapies (eg, chemotherapy) or the disease itself.

Thus, the optimal patient population for sipuleucel-T treatment may be those with a low disease burden and an immune system uncompromised by disease and/or prior therapy. Data from recent post hoc analyses subdividing the IMPACT patient population by baseline PSA level support this approach. Although the study was not powered to show significance within each quartile (due to small patient numbers), it was found that patients in the lowest quartile (ie, those with ≤ 22.1 ng/mL baseline PSA) had the greatest magnitude difference in median OS: a 13.0-month improvement with sipuleucel-T vs control (41.3 months vs 28.3 months; HR = 0.51; 95% CI, 0.31–0.85). By comparison, patients in the upper quartile (> 134.1 ng/mL baseline PSA) had a 2.8-month improvement in median OS with sipuleucel-T vs control (HR = 0.84; 95% CI, 0.55–1.29).43

In another analysis, product characteristics of sipuleucel-T were compared across studies of patients with a range of disease states (neoadjuvant, earlier asymptomatic or minimally symptomatic metastatic CRPC, and metastatic CRPC).44 The results showed that although sipuleucel-T could be successfully produced for patients across all disease settings, those in earlier treatment settings showed more favorable product parameters, including CD54 upregulation. As this latter parameter has been shown to positively correlate with OS, these data further suggest that patients in early disease settings may derive the greatest benefit from treatment. Thus, treatment with sipuleucel-T as early as possible following detection of metastatic disease may yield optimal results.

**Drug-Sequencing Strategies**

Optimal timing of newer treatments for CRPC, such as sipuleucel-T, may not be obvious. Clinical decisions regarding drug sequencing become increasingly complex with the expansion of treatment choices for metastatic CRPC, as new drugs become commercially available (eg, abiraterone acetate, enzalutamide, and radium-223). Although trials are underway to evaluate various drug-sequencing approaches with some of these newer treatments, no data are currently available to guide such decisions. Therefore, in the practical setting, drug-sequencing decisions are subject to heuristic factors and are based on the physician’s interpretation of the disease setting at which the best medical risk-to-benefit ratio could be achieved, the potential susceptibility of the tumor to various treatments, and the commercial cost vs survival impact for each patient.

Within the context of the current metastatic CRPC treatment paradigm, points at which sipuleucel-T may be integrated could be defined as follows: directly after androgen deprivation therapy (ADT) failure, after failure of secondary hormonal therapy and prior to docetaxel therapy, or after docetaxel therapy. As previously highlighted, one might argue that sipuleucel-T should be used earlier in the treatment paradigm and temporally separated from corticosteroid use, due to the immunologic mechanism of action.

In the early setting (eg, soon after ADT failure), patients are not likely to have received immunosuppressive or cytotoxic chemotherapies and are more likely to have a lower disease burden than patients in later settings will have. Thus, in comparison to patients with later-stage disease, early-stage patients are likely to have a more robust immune system and slower disease kinetics, affording the best opportunity for an immune response to develop prior to exposure to corticosteroids or chemotherapy.

There is a rationale for concurrent use of sipuleucel-T with agents such as bicalutamide, nilutamide, estrogen, or low-dose ketoconazole without hydrocortisone. To begin, there may be some desire to induce PSA responses in early settings, which could be accomplished with hormone therapies. Additionally, there is evidence suggesting that ADT may have effects on the immune system, which could enhance the activity of sipuleucel-T and other immunotherapies.45 Of note, however, immunosuppressive effects have been suggested to be associated with ketoconazole.46-48

Currently, no clinical trial data are available on sipuleucel-T following failure of new-generation secondary hormonal therapies, such as abiraterone acetate and enzalutamide. As highlighted previously, the presumably higher disease burden of such patients suggests that the effect of sipuleucel-T treatment would be of a lower magnitude in this setting than in the post-ADT setting. Data from the IMPACT trial showed a trend toward greater benefit among patients treated prior to secondary hormone therapy (ie, castration alone) compared with those who received combined androgen blockade.15 It is possible that this difference in treatment effect could be accentuated for newer hormonal agents administered for an extended period. Thus, sipuleucel-T treatment may not be optimal in this setting. However, sipuleucel-T may be appropriate for patients following secondary hormonal therapy if their disease burden is relatively low and they are not likely to require chemotherapy for 3 months or more.

Although sipuleucel-T is likely to be most effective in the predocetaxel setting, data from the phase III clinical trials have shown that patients who have received prior docetaxel should not be precluded from sipuleucel-T treatment. In the IMPACT trial, 15.5% of patients received docetaxel prior to sipuleucel-T.19 Data from a subanalysis of these patients suggested that those who received prior docetaxel are capable of generating immune responses and may experience a survival
benefit. Of note, these patients had received docetaxel at least 3 months prior to study enrollment. Given the disease kinetics of most patients following docetaxel treatment, a 3-month wait period for the next therapy may not be possible, in which case other treatments should be considered if the patient is not thought to be an appropriate candidate for sipuleucel-T therapy. However, several questions remain unanswered regarding the drug sequencing of sipuleucel-T within the CRPC treatment paradigm. What is the appropriate sequencing of sipuleucel-T with emerging therapies such as radium-223, which have a direct impact on bone marrow production of leukocytes? How should it be sequenced with secondary or later-generation hormone-axis drugs (eg, estrogens, cytochrome inhibitors, abiraterone acetate, and enzalutamide) or with drugs that are partnered with daily oral corticosteroids (eg, abiraterone acetate, docetaxel, cabazitaxel, and others)? Currently, no data are available that directly answer these questions, yet ongoing studies may address some of them, and guidance can be gleaned from available data.

Combination therapy with sipuleucel-T and abiraterone acetate plus prednisone is currently being evaluated in a randomized phase II trial of patients with asymptomatic or minimally symptomatic metastatic CRPC (NCT01487863). In this trial, concurrent treatment with sipuleucel-T and abiraterone acetate plus prednisone will be compared with sequential treatment of sipuleucel-T followed by abiraterone acetate plus prednisone. Again, along with the strong scientific rationale for combining these two treatments is a consistent observation that suppression of testosterone may yield immunostimulatory effects. Additionally, data from a trial of sipuleucel-T in the neoadjuvant setting demonstrated lymphocyte infiltration at the site of disease in patients treated with sipuleucel-T compared with controls, supporting the immunologic mechanism of action. Collectively, these findings suggest that sipuleucel-T is biologically active in these early settings. OS results from trials in earlier disease settings are eagerly awaited.

**Future Directions**

**Other Prostate Cancer Populations**

Could patients in the premetastatic setting respond differently to sipuleucel-T compared with patients with metastatic disease? Based on the exploratory analyses described here, it seems possible that such patients would derive greater benefit than those whose disease has already progressed to metastatic CRPC. As highlighted previously, studies of sipuleucel-T in patients with nonmetastatic prostate cancer and a rising PSA level (PROTECT [NCT00779402] and P10-2 [NCT01431391]) and in the neoadjuvant setting (NeoACT [NCT00715104]) are underway.

Beer et al reported results from the randomized phase III PROTECT trial in which postprostatectomy patients with hormone-responsive prostate cancer and a rising PSA level were treated with sipuleucel-T (n = 117) or control treatment (n = 59). The primary trial endpoint was time until PSA reached at least 3.0 ng/mL. Although it favored the investigational treatment arm, the difference was not significant (18.0 vs 15.4 months; P = .737). However, PSA doubling time was significantly longer in the sipuleucel-T arm (155 vs 105 days; P = .038).

Additionally, data from a trial of sipuleucel-T in the neoadjuvant setting demonstrated lymphocyte infiltration at the site of disease in patients treated with sipuleucel-T compared with controls, supporting the immunologic mechanism of action. Collectively, these findings suggest that sipuleucel-T is biologically active in these early settings. OS results from trials in earlier disease settings are eagerly awaited.

**Combination Therapy and Target Modulation**

One potential area for development is in evaluating whether induction treatment with radiotherapy or with other cytotoxic and hormonal treatments may enhance the activity of sipuleucel-T. As for most pivotal trials introducing new treatments, the IMPACT trial of sipuleucel-T had few preparatory requirements except the inclusion criterion, specifying no recent corticosteroids or chemotherapy, and a minimum white blood cell count of ≥ 2,500/μL. This approach allowed for a definitive evaluation of the sipuleucel-T treatment effect but did not address whether certain treatments in combination with sipuleucel-T (either concurrently or sequentially administered) may have additive or synergistic effects.

As discussed previously, there is a rationale for combining sipuleucel-T with hormone suppression based on the potential immunostimulatory properties of the latter, and current studies are testing such combinations: one with leuprolide acetate (NCT01431391) and another with abiraterone acetate (NCT01487863). Besides hormone suppression, the palette of drugs with other mechanisms of action that mediate tumor regression is considerably broader in 2012 than when the IMPACT trial and D9902A and D9901 trials were conceptualized a de-
Cancer Control January 2013, Vol. 20, No. 1

Response against HER2/neu. This product is manufactured by Dendreon Corporation.

**Other Antigen Targets**

**Modulation of the Immune Environment**

As noted previously, although the antigen-presentation step in the manufacture of sipuleucel-T is distinctly ex vivo, the ultimate immune response occurs in vivo, in the patient’s own tumor-influenced immune context. Thus, the growing awareness of the direct impact of the tumor cell burden on immune function (eg, through release of inflammatory cytokines, abundance of regulatory T cells, burden of senescent T cells, phenotypic dendritic cell modulation favoring tolerance) defines a variety of possible directions for improving the sipuleucel-T treatment effect.

Several pharmaceutical approaches, including some marketed products, can influence the immune microenvironment and may offer opportunities for rational combinations with sipuleucel-T. Selected examples of such agents include those that may decrease the burden of immunosuppressive regulatory T cells (eg, cyclophosphamide68 and sunitinib69) and those that promote breakage of immune tolerance by either modulating the dendritic cell phenotype60 (eg, all-trans-retinoic acid,61 triterpenoids,62 and Toll-like receptor ligands63) or blocking immune checkpoints affecting T-cell deactivation (eg, ipilimumab or anti-PD-1 [BMS 965538/MDX1106]64).

Conclusions

The landscape of treatment for castration-resistant prostate cancer (CRPC) integrating hormonal therapy, chemotherapy, targeted agents, radiopharmaceuticals, and other immune strategies will continue to evolve and so may the application of sipuleucel-T. With the April 2010 approval by the US Food and Drug Administration of sipuleucel-T as a novel treatment of asymptomatic and minimally symptomatic metastatic CRPC, immunotherapy has emerged as a standard of care option with a survival impact. Data from the phase III randomized IMPACT trial65 spanning a decade showed improved median overall survival (25.8 vs 21.7 months) and hazard ratio for death (0.78). Although classic measures of disease progression such as objective response and progression-free survival are not reliable markers of sipuleucel-T activity, other pharmacodynamic indicators may prove to be useful in providing treating clinicians with immediate feedback from the treatment. Thus, for patients with asymptomatic or minimally symptomatic metastatic CRPC, with disease features closely paralleling those required for participation on the pivotal trial, sipuleucel-T may be an option.

Many questions remain regarding where sipuleucel-T best fits in the treatment paradigm and how it should be sequenced with other therapies. Current data seem to indicate that sipuleucel-T may yield greatest benefit in patients with CRPC who are early in their disease course. Thus, it could be reasoned that sipuleucel-T should be administered to patients soon after androgen deprivation therapy failure. However, other disease management options, including the newest hormone-related drugs such as abiraterone and enzalutamide, will be available for physicians to consider either prior to or following sipuleucel-T administration. The complexity of treatment decisions will not be directly solved. We hope that the emergence of sipuleucel-T for prostate cancer will be a starting point for effective application of other immune treatments building on more antigens as well as for strategic coordination with nominally nonimmunemediated treatments.69

Johnathan C. Maher, PhD, of Dendreon Corporation contributed to the writing and editing of the submitted work. The authors were fully responsible for all content and editor-
rial decisions; contributed to the conception and design of the manuscript, data analysis and interpretation, writing and editing of the manuscript, and approved the final version for submission.

References


