PROVENGE (Sipuleucel-T) in Prostate Cancer: The First FDA Approved Therapeutic Cancer Vaccine

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Conflicts of interest: Cheever, None; Higano is a Dendreon investigator and consultant.

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Abstract

Sipuleucel-T (PROVENGE) is the first therapeutic cancer vaccine approved by the FDA. In men who have metastatic castration-resistant prostate cancer with no or minimal symptoms, sipuleucel-T prolongs median survival by 4.1 months compared to those treated with placebo. At 3 years, the proportion of patients in the vaccine group who were alive was 50% higher than that in the control group (31.7% vs. 21.7%, respectively). Sipuleucel-T, designed to elicit an immune response to prostatic acid phosphatase, uses the patient’s own immune system to recognize and combat his cancer. Currently, there are no other agents that offer a survival benefit in this population of asymptomatic patients who have not been treated with chemotherapy except docetaxel, which due to its inherent toxicities, many patients and physicians often delay until symptoms develop. Straightforward strategies to increase the efficacy of sipuleucel-T are likely to provide even greater benefit. The preclinical and clinical development of sipuleucel-T is reviewed and approaches to enhance efficacy are considered herein.
Introduction

In April of 2010, the US Food and Drug Administration (FDA) approved PROVENGE® (sipuleucel-T), an autologous cellular immunotherapy, for the treatment of patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC). Sipuleucel-T is a therapeutic vaccine formulated to stimulate an immune response to prostate cancer cells by targeting prostate acid phosphatase (PAP), a tissue antigen expressed by prostate cancer cells (1). The therapeutic intent is to generate PAP-specific T cells capable of recognizing and killing prostate cancer cells that express PAP. After radical prostatectomy, the major remaining source of PAP in the body is the cancerous prostate tissue. The PAP vaccine immunogen is formulated as PA2024, a fusion protein combining recombinant PAP with recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF). The PAP-GM-CSF fusion protein is incubated with autologous peripheral blood mononuclear cells (PBMC) obtained by leukapheresis. The GM-CSF is used to activate antigen presenting cells (APCs) within the autologous PBMC product (2-5). The activated APCs are capable of activating and inducing replication of PAP-specific immune T cells with the capacity to recognize and kill PAP-positive prostate cancer cells. Three days after the leukapheresis and after approximately 40 hours of incubation, the cells are washed to remove the fusion protein, shipped to the patient care site, and infused into the patient as the sipuleucel-T product.

Preclinical data

The prostate gland varies greatly between species (6) and immune systems differ; thus, the results from animal models cannot be directly extrapolated to prostate vaccine trial design in humans. However, immunizing rats with rat prostate tissue antigens has been shown to induce
destructive prostatitis (7), and a formulation using rat APCs loaded with rat PAP plus GM-CSF induced rat prostatitis (8) without apparent toxicity to normal non-prostate tissues. Thus, overcoming normal immune tolerance and induction of autoimmunity to prostate tissue was shown to be possible (7, 8). Although the prostate gland in rats was not totally destroyed by the PAP vaccine despite induction of autoimmune prostatitis, vaccine induction of prostatitis in rats laid the groundwork for clinical trials of similar vaccines against prostate cancer.

**Clinical studies**

**Early-phase trials:** Sequential phase I and II studies evaluated safety and the ability to circumvent immune tolerance to PAP (9, 10). The patients in the phase I trial received increasing doses of sipuleucel-T. Those on the phase II protocol received doses totaling their entire leukapheresis product prepared as sipuleucel-T. Fever, experienced by 14.7% of patients, was the most common adverse event (AE). All 31 patients tested (100%) showed an immune response to the fusion protein, PA2024, and 38% showed an immune response to PAP. Time to progression was correlated to both dose and immune response to PAP. With tumor response measured as decreased levels of prostate-specific antigen (PSA) (≥25%) from baseline, tumor response was seen in only 20% of patients. Of note, the fusion protein contains a joining region segment that is not expressed by normal PAP or GM-CSF and can therefore be recognized as “foreign” by the patient’s immune system. Elicitation of an immune response to this foreign joining region segment is expected and is a sign of immune competence, but is most likely irrelevant to the therapeutic outcome. Detection of immunity to PAP is a more important potential marker of therapeutic immune response. An additional efficacy trial, testing a vaccine containing autologous CD54-positive PA2024-loaded APCs, provided similar results (11). CD54, also
referred to as intercellular adhesion molecule-1 (ICAM-1), is an activation marker for APCs and other white blood cells (12).

**Phase III studies:** Two phase III studies (D9901 and D9902A) set the stage for the IMPACT trial, the pivotal study that led to FDA approval (13, 14). Both were randomized, double-blind, placebo-controlled trials of patients with asymptomatic mCRPC. The designated primary endpoint was median time to observed disease progression with a planned analysis of overall survival as a secondary endpoint.

The control was autologous PBMC obtained by leukapheresis, but the PBMC were cultured without the PAP-GM-CSF fusion protein (i.e., without either antigen or the activating effect of GM-CSF). Only one-third of the leukapheresis sample was processed for each dose of the control formulation. The remainder of the PBMC were cryopreserved and held in reserve for possible use in a planned salvage vaccine study. The control product was denoted as APC8015F.

For D9901, the median time to disease progression was 11.7 weeks for the sipuleucel-T arm vs. 10.0 weeks for the control arm. The curves separated at 8 weeks and showed a persistent separation throughout the rest of the study. However, the difference favoring sipuleucel-T was just short of statistical significance ($P=0.052$). The median overall survival was 112 weeks for sipuleucel-T compared to 93 weeks for the control arm. The increase in overall survival favoring sipuleucel-T of 4.5 months was significant ($P=0.01$) (3, 13).
The positive effect on overall survival appeared to be inconsistent with the lack of detectable effect on median time to disease progression, suggesting that median time to disease progression might not be appropriate for measuring vaccine effect in patients with very short times to disease progression. Based on the 3-vaccination regimen, one would anticipate that the optimal immune response would not occur or be operative until the third vaccination (i.e., after 4 weeks of therapy). With a median time to progression of 10 to 11 weeks, the optimal immune response would have had only 6 to 7 weeks to operate before the observed progression. The time might be too short to expect a prolongation in time to progression in spite of the ultimate demonstration of a vaccine-induced prolongation in median survival. In addition, the time of progression is difficult to precisely determine in prostate cancer. New lesions on bone scans may be interpreted as progression when even when the disease is responding (i.e., flare phenomenon) and the combination of rising PSA and supposed bone scan progression could erroneously lead to a designation of progression. More recent progression guidelines devised by the Prostate Cancer Working Group 2 have been designed to prevent this situation, based on results from this and other immunotherapy trials (15).

For the second randomized phase III study, D9902A, time to progression was also not statistically different (10.9 weeks vs. 9.9 weeks). The median survival was again prolonged in the sipuleucel-T arm compared to the control arm (15.7 months vs. 9.0 months, respectively) and survival at 3 years was 50% higher (32.3% vs. 21.2%, respectively). Despite the clear benefit in overall survival at 3 years, prolongation of median survival was not significant ($P=0.331$) (3, 13, 14). The median time to progression occurred on average only 6 weeks after the third vaccination, approximately 1 year before the median survival time.
The third randomized phase III trial, D9902B, also called IMPACT (IMmunotherapy Prostate AdenoCarcinoma Treatment) led to FDA approval (16). The primary endpoint was overall survival. IMPACT was a double-blind, placebo-controlled study with 512 asymptomatic or minimally symptomatic patients with mCRPC randomly assigned 2:1 to sipuleucel-T (n=341) or control (n=171). Sipuleucel-T was administered every 2 weeks for three total doses. Of the 330 patients who received sipuleucel-T, 92% received all three infusions vs. 93% in the control arm. Comparing treatment and control arms, the median overall survival was 25.8 months vs. 21.7 months, respectively ($P=0.032$), with a median survival benefit of 4.1 months. The adjusted hazard ratio for death was 0.78 (95% CI, 0.61-0.98). The Kaplan-Meier estimate for overall survival for both groups at 36 months was 31.7% vs. 23.0%, respectively, a 38% increase in survival at 3 years (16) (Figure).

The Halabi prognostic model can be used to predict individual survival probabilities of patients with metastatic hormone-refractory prostate cancer (17). The model is predicated on factors linked to outcome, including lactate dehydrogenase, PSA, alkaline phosphatase, Gleason sum, Eastern Cooperative Oncology Group performance status, hemoglobin, and the presence of visceral disease. The median overall survival predicted by the Halabi prognostic model was 20.3 months for the treatment arm vs. 21.2 months for the control arm (3), providing additional support of the efficacy of sipuleucel-T. Between the three phase III studies, the therapeutic outcome was equivalent for overall survival in the intent-to-treat population (14) (Table). Despite the demonstrated effect on overall survival, only one sipuleucel-T–treated patient had evidence of measurable response with a partial remission.
As in the prior smaller phase III trials, the median time to objective disease progression was short, 14.6 weeks vs. 14.4 weeks ($P=0.63$). PSA reductions of at least 50% compared to baseline were confirmed 4 weeks later in only 8 of 311 (2.6%) of sipuleucel-T–treated patients as opposed to 2 of 153 (1.3%) in the placebo group. In a double-blind, randomized, placebo-controlled study (P-11), 176 men with a rising PSA after prostatectomy received hormonal therapy followed by vaccine or control (18). Sipuleucel-T did not significantly delay cancer progression, defined as PSA reaching 3.0 ng/mL. However, the rate of PSA rise was slower in patients who received the vaccine. These results support the presumption that the vaccine-induced therapeutic response continues to function after the median time to progression. Changes in PSA doubling times were not reported in the IMPACT trial.

Open-label vaccine in control patients: The pivotal trials permitted crossover of placebo patients when progression was determined by central review. This design may have decreased the ability to measure the true positive magnitude of the therapeutic effect of sipuleucel-T. The vaccine used to treat placebo patients who crossed over to the open-label vaccine protocol (16) differed in formulation from sipuleucel-T in that the vaccine (APC8015F) was processed from the frozen PBMC collected during the original leukapheresis. Patients could be treated at the time of initial progression or any time thereafter, including after chemotherapy. APC8015F was manufactured according to the same specifications as sipuleucel-T using the PAP-GM-CSF fusion protein. However, fewer total cells were injected. On the control arm, 109 of 171 patients (64%) received therapy with the salvage vaccine, APC8015F. Although those treated with APC8015F had an estimated median survival of 23.8 months vs. 11.6 months for those who did not, it is difficult to
draw any conclusions regarding efficacy, since therapy was not randomly assigned. The activity of APC8015F has not been prospectively studied.

Approximately 50% of patients in each arm were treated with docetaxel following progression (16) and therefore the difference in survival seen in the sipuleucel-T arm is not due to an imbalance of patients who received docetaxel.

**Acute infusion reactions:** The majority of patients (71%) experienced acute infusion reactions. Most events were mild or moderate. The most common events occurring in ≥20% of patients were chills, pyrexia, and fatigue. These events generally occurred within 1 day of an infusion, were managed on an outpatient basis, and most resolved within 2 days. Severe (grade 3) acute infusion reactions were reported in 3.5% of patients and included chills, fever, fatigue, asthenia, dyspnea, hypoxia, bronchospasm, dizziness, headache, hypertension, muscle ache, nausea, and vomiting. No grade 4 or 5 acute infusion reactions were reported (19). Of note, only 3 of 338 patients (0.9%) in the pivotal trial (16) were unable to receive all three infusions because of infusion-related AEs.

**Integrated safety analysis:** Other than an analysis of acute infusion reactions, the integrated safety analysis endorsed by the FDA and presented in the Biologic License Application (BLA) (4) and the package insert (19) was summarily unhelpful for the prescribing physician. The integrated safety analysis (19) was based on 601 patients who had received at least one leukapheresis procedure in four randomized controlled trials (D9901, D9902A, D9902B, and P-11) (3). The integrated safety analysis presented adverse reactions during the entire time of the
study. Therefore, a substantial but indeterminate portion of the AEs occurred late after the vaccine and were equivalent in both the vaccine and control arms, strongly implying that the AEs described were more likely due to the disease than to the vaccine.

Cerebrovascular events were observed in 2.4% of the sipuleucel-T–treated patients vs. 1.8% of the control patients. Since most occurred more than 6 months after the last infusion, the significance of this finding in relation to the vaccine remains unclear. The FDA is requiring a post marketing registry of approximately 1,500 patients to further assess cerebrovascular risk.

**Processing and Character of the Product**

Processing involves separating the blood mononuclear cells from other blood-born white blood cells using proprietary technology and incubation with the PAP-GM-CSF fusion protein. Patient PBMC are obtained via standard leukapheresis and shipped to a Dendreon manufacturing site. There, the PBMC are fractionated and incubated with the PAP-GM-CSF fusion protein.

GM-CSF stimulates the growth and activation of APCs, such as macrophages and dendritic cells (3-5). In turn, the APCs activate other cells in the culture, such as T cells. PAP is taken up by activated APCs and processed into a form recognizable by T cells (i.e., small peptides bound to major histocompatibility complex [MHC] molecules on the cell surface). The activated APCs incubated with PAP are washed and suspended in Lactated Ringer’s Injection, USP, for infusion back into the patient. Specifications for the release of sipuleucel-T for infusion are based on sterility results and cell counts of at least 50 million CD54+ cells. The median product contains $1.9 \times 10^9$ CD54+ cells, with a range from $0.108 \times 10^9$ to $8.600 \times 10^9$ (3). Dendreon has demonstrated
that biologic activity is present in the CD54 fraction. Thus, upregulation of CD54 on the monocyte-rich population serves as the potency assay for the product manufacture (3) and may correlate with improved survival.

The final sipuleucel-T product is heterogeneous and varies from dose to dose within each patient. Sipuleucel-T was designed as a vaccine composed of mature APCs loaded with PAP, however, the product also contains many other cell types including T cells, B cells, and natural killer cells. The final mixture of cells depends on the composition of the individual patient’s leukapheresis product and the outcome of processing. Both change with each subsequent leukapheresis. The product derived from the first leukapheresis is returned for intravenous administration on day 3. On approximately days 14 and 28, the patient undergoes leukapheresis again to manufacture the second and third doses of sipuleucel-T. Although the manufacturing process is identical, the second and third doses are biologically quite different from the first. Each dose contains progressively more activated APCs as well as more PAP-specific T cells with the capacity to recognize and kill prostate cancer cells (20).

**Mechanism of Therapeutic Efficacy**

The designated purpose of sipuleucel-T is to elicit a therapeutic immune response to PAP expressed by cancer cells. The first treatment primes the immune system. Sipuleucel-T activates APCs ex vivo. The activated APCs facilitate both ex vivo priming of T cells during culture and in vivo priming after administration. After infusion of the first dose, there is a detectable increase in APC and T-cell activation markers in the PBMC of treated patients and an increase in the ex vivo production of T-cell activation-associated cytokines (20). Studies examining cytokine
secretion from PBMC during the culture of each leukapheresis product demonstrate progressive activation of APCs and T cells. An analysis of the culture supernatant from PBMC from each leukapheresis showed increases in APC activation cytokines (IL-1a, IL-1b, MIP1a, MIP1b, and IL-23), T-cell activation-associated cytokines (IL-2, IL-3, IL-4, IL-5, IL-10, and IL-17), and APC/T-cell activation-associated cytokines (IL-12p70, interferon-gamma, and tumor necrosis factor alpha). Thus, increasingly activated APCs and T cells are infused into the patients (20).

Detecting PAP-specific responses in the patients and correlating PAP-specific immune responses to outcome are more problematic. PAP-specific antibody responses that exceeded the designated low value of 400 at any time after baseline were observed in only 43 of 151 patients (28.5%) in the sipuleucel-T arm vs. 1 of 70 patients (1.4%) in the placebo arm. At week 6, T-cell proliferation responses (stimulation index >5) to PAP were observed in only 15 of 55 patients (27.3%) in the sipuleucel-T arm vs. 2 of 25 patients (8.0%) in the placebo group (16).

Sipuleucel-T prolonged survival, but without a clear demonstration of detectable PAP-specific immunity in the majority of patients. Accordingly, a subset of patients without detectable immune responses appeared to benefit from the vaccine. The apparent benefit of the vaccine in patients without detectable immune responses mitigates against detecting a correlation of outcome to PAP immunity.

A low incidence of detectable antibody response is expected from any activated APC vaccine. The activated APCs in sipuleucel-T are known to process and degrade PAP for presentation to T cells. Due to the washing process, exceedingly little free PAP in protein form (the
configuration needed to elicit antibody responses) is injected into patients. The dearth of
detectable T-cell responses to PAP might be explained by the fact that responses were assayed
from peripheral blood. Peripheral blood might not adequately represent T-cell responses at sites
of tumor deposition. Alternatively, although unlikely, it is possible that substantial numbers of
PAP-specific T cells were not activated in most patients and thus the demonstrated therapeutic
effect was not related to or dependent upon elicitation of PAP-specific immune responses.
Additional studies are needed to determine the proximate mechanisms of efficacy.

One might speculate that mechanisms other than or in addition to the slowing of tumor growth
were responsible for the improved outcomes. This begs the question of “Why do patients with
prostate cancer die?” and the corollary “What was the proximal cause of death impacted by
sipuleucel-T?” In general, patients with cancer die of combinations of organ failure, infection,
and cachexia. Specifically for prostate cancer, patients commonly have dominant pain and
cachexia. The proximal cause of death in the sipuleucel-T trials was not reported. However, in
general, approximately 60–70% of patients with advanced prostate cancer have cachexia (21-23).
Several cytokines (e.g., TNFa, IL-1, IL-6, and IL-8) are elevated in patients with prostate cancer
and may be involved in cachexia (21). Infusing activated APCs and T cells, as components of
sipuleucel-T, may have substantially perturbed the character and level of these circulating
cytokines without noticeably affecting tumor size or growth.

Advantages Over Other Vaccines in Development and Chemotherapy

Vaccines: Sipuleucel-T is the first FDA-approved vaccine for cancer. Thus, there is no approved
direct comparator vaccine. However, an alternative well-tolerated recombinant Poxvirus-based
PSA-targeted vaccine (PROSTVAC-VF) in development could prove to have substantial efficacy. Overall survival analysis of a phase II, randomized, controlled trial in patients with mCRPC was associated with a 44% reduction in death rate and an 8.5-month improvement in median overall survival (24). The data strongly suggest therapeutic benefit but need confirmation through a phase III study. From preliminary data, the study investigators hypothesize that patients with more indolent mCRPC (Halabi predicted survival ≥18 months) may best benefit from PSA-specific vaccine therapy (24). As with sipuleucel-T, there was no significant prolongation of median survival.

Chemotherapy: To date, chemotherapy has shown only modest benefit in patients with mCRPC. In two phase III studies (TAX 327 and SWOG 9916) docetaxel-based regimens have shown a survival advantage (25, 26). In TAX 327, the pivotal trial for docetaxel approval, the median survival was 18.9 months in the every-3-week docetaxel arm compared to 16.4 months in the mitoxantrone arm, with a hazard ratio of 0.76 or a 2.5-month improvement in median survival (25). The most significant grade 3–4 AEs were neutropenia (32%), infection (6%), anemia (5%), sensory neuropathy (2%), motor neuropathy (2%), nausea (3%), diarrhea (2%), vomiting (2%), dyspnea (3%), fatigue (5%), and arthralgia (1%). Patients reported lower grade, but nonetheless disturbing, side effects of fluid retention (24%) with peripheral edema (18%) and weight gain (8%), and sensory neuropathy (30%), motor neuropathy (7%), alopecia (65%), nail changes (41%), diarrhea (32%), stomatitis/pharyngitis (20%), taste disturbance (18%), nausea (17%), and fatigue (53%). In the supporting phase III SWOG 9916 trial, the median survival advantage was 1.9 months (17.5 months for the docetaxel plus estramustine arm vs. 15.6 months for the mitoxantrone plus prednisone arm) with a hazard ratio of 0.80 (26). Based on these modest
survival data and the toxicity profile of docetaxel, it is clear why both patients and physicians are reluctant to use chemotherapy in men who have no or few symptoms related to mCRPC.

Conclusions
At the present time, sipuleucel-T is the only therapy that is specifically approved for men with asymptomatic or minimally symptomatic mCRPC. The very acceptable toxicity profile makes sipuleucel-T an attractive option for such patients, particularly compared to treatment with docetaxel. While a significant proportion of patients taking sipuleucel-T will undoubtedly receive docetaxel at a later stage in the disease, the availability of a therapy that improves survival at an earlier stage is a welcome addition to treatment options for patients with mCRPC. Guidelines from the National Comprehensive Cancer Network (NCCN) now include sipuleucel-T in the treatment options for men with mCRPC with no or minimal symptoms (27).

One of the current challenges with sipuleucel-T is determining when in the course of prostate cancer it should be used. The FDA-approved package insert states that sipuleucel-T “is indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.” The label gives little additional guidance for use. Specifically, patients treated with chemotherapy are not excluded from receiving sipuleucel-T, yet many such patients continue on low-dose prednisone as a component of their prior chemotherapy. Because of the potential detrimental effects on the immune system, corticosteroid use was excluded in the clinical trials and hence, should be stopped before treating a patient with sipuleucel-T. In general, sipuleucel-T should be utilized before chemotherapy, except in cases where disease remains stable after chemotherapy without the use of steroids.
It is anticipated that abiraterone, an investigational CYP17 inhibitor, will be approved by the FDA in 2011. Abiraterone has been studied in two phase III trials that are fully accrued and maturing, one in asymptomatic patients before receiving docetaxel (COU-AA-301), and the other in patients who have been previously treated with docetaxel (COU-AA-302). The basis for this phase III program was the significant activity seen in early phase trials (28-30). The interim results of COU-AA-302 were recently presented (31), demonstrating that abiraterone plus prednisone was superior to placebo plus prednisone in terms of overall survival (14.8 months vs. 10.9 months, HR 0.65), the primary endpoint. Based on these results, regulatory approval is anticipated for abiraterone in patients who have received docetaxel. Given the survival benefit seen in those who have received chemotherapy, it is anticipated that COU-AA-301 will also be positive, leading the way for approval in the asymptomatic CRPC population where sipuleucel-T is also approved.

Assuming that abiraterone will eventually be FDA approved for those with asymptomatic CRPC either before or after docetaxel, it will be important to consider the appropriate timing of sipuleucel-T with respect to abiraterone. Because abiraterone was studied in combination with low-dose prednisone, approval will include concurrent use of prednisone to prevent the mineralocorticoid effects of hypertension and hypokalemia seen in some patients on abiraterone alone. Since abiraterone must be administered with prednisone, it seems logical that sipuleucel-T would be administered before abiraterone and that the administration of any therapy that includes prednisone would be delayed for as long as possible due to the immunosuppressive effects of corticosteroids. Although some literature suggests that abiraterone can be given without
prednisone (32), use as a single agent is not advised until better data are presented and guidelines about this practice are developed.

A confusing issue for patients and clinicians alike is the lack of the usual response criteria after administration of sipuleucel-T. Neither PSA level nor time to progression were significantly impacted after sipuleucel-T. Therefore, there should be no expectation that PSA will decline or that imaging studies will improve after treatment. The lack of response indicators also means that the physician cannot advise the individual patient whether or not he has benefited from receiving sipuleucel-T, only that there is a population benefit in terms of overall survival. This is similar to the logic used in adjuvant therapy of breast or colon cancers. In addition, sipuleucel-T is not indicated for the treatment of patients who have symptoms of metastatic disease. At this writing, there is no evidence of survival benefit or indication of palliative benefit of sipuleucel-T given as a single agent to patients with symptomatic mCRPC.

Clinical development of sipuleucel-T for FDA approval began with the first patient treated in 1997. Thus, the formulation and regimen have been “locked” and unchanged for 13 years. The locked regimen chose to administer three doses of sipuleucel-T over approximately 4 weeks. Given the comparative efficacy and limited toxicity, studies to increase the efficacy of sipuleucel-T are warranted. Simple methods likely to increase the efficacy include (1) administering sipuleucel-T more than three times to boost and extend the response, (2) treating patients earlier in their disease course, extending immune response time against a lower number of cancer cells, and (3) combining sipuleucel-T with immune response agents known to activate, accelerate, and augment immune responses. Multiple strategies involving
targeted agents might also have substantial effects facilitating T-cell entry into tumors and thus efficacy. One study was conducted combining the vaccine with bevacizumab in patients after definitive therapy, but was too small and the single arm design precluded insights into how the agents combine (33).

Immunotherapy agents with known immunologic efficacy that could likely increase the efficacy of sipuleucel-T include T-cell growth factor (IL-7) to increase the number and repertoire of naive T cells, T-cell growth factor (IL-15) to increase the growth and survival of immune T-cell growth factors (Flt-3Ligand) to increase the number of APCs, agonists to activate dendritic cells and other APCs (CD40Ligand), adjuvants (IL-12, CpG, MPL) to augment T-cell responses, agonists to activate and stimulate T cells (anti-CD137), inhibitors of T-cell checkpoint blockade (anti-CTLA4, anti-PD1), and agents to inhibit, block, or neutralize cancer cell and immune cell-derived immunosuppressive cytokines (anti-IL-10, anti-TGF-beta, 1-methy-tryptophan). These and similar agents in the same categories have been discovered, invented, constructed, and proven to have immunologic function in both animal models and human clinical trials (34). In the past, it has been extremely challenging, if not impossible, to combine investigational immunotherapeutic agents owned by different sponsors, due to a variety of regulatory and legal hurdles. With the commercial availability of sipuleucel-T and perhaps other promising vaccines in the future, testing and developing agents designed to activate, augment, and extend immune responses can proceed with the hope of refining and improving immunotherapeutic outcomes in patients with prostate cancer and other solid tumor malignancies.
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## Table: Summary of Overall Survival Results for Three Phase III Randomized Trials

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<td>Placebo (N=171)</td>
<td>Sipuleucel-T (N=82)</td>
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<tr>
<td>Median, months (95% CI)</td>
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<td>21.7 (17.7, 23.8)</td>
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<td>Hazard Ratio (95% CI)</td>
<td>0.775 (0.614, 0.979)</td>
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<td>0.786 (0.484, 1.278)</td>
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<td>(P)</td>
<td>0.032*</td>
<td>0.010 b</td>
<td>0.331 b</td>
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Test statistic based on the Cox proportional hazards model adjusted for PSA (1n) and LDH (1n) and stratified by bisphosphonate use, number of bone metastases, and primary Gleason grade.

bHazard ratio based on the unadjusted Cox proportional hazards model and \(P\) values based on an unprespecified test (log-rank)

Abbreviations: CI, confidence interval; LDH, lactate dehydrogenase; PSA, prostate-specific antigen

From Biologics License Application SNT125197 (3)
Figure 1: The results of the primary efficacy analysis of treatment with sipuleucel-T as compared with placebo (hazard ratio for death in the sipuleucel-T group, 0.78; 95% confidence interval [CI], 0.61-0.98; *P*=0.03). (Figure derived from Kantoff et al. 16. *Copyright © 2010 Massachusetts Medical Society. All rights reserved.*)
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HR = 0.775 (95% CI, 0.614, 0.979)  
P = 0.032 (Cox model)  
Median survival benefit = 4.1 months  

Sipuleucel-T:  
Median survival: 25.8 months  
36-mo. survival: 31.7%  

Control:  
Median survival: 21.7 months  
36-mo. survival: 23.0%  

Percent survival
Clinical Cancer Research

PROVENGE (Sipuleucel-T) in Prostate Cancer: The First FDA Approved Therapeutic Cancer Vaccine

Martin A Cheever and Celestia Higano

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