Original Article

Integrated Data From 2 Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trials of Active Cellular Immunotherapy With Sipuleucel-T in Advanced Prostate Cancer

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BACKGROUND: Sipuleucel-T is an investigational active cellular immunotherapy product designed to stimulate an immune response against prostate cancer. The safety and efficacy of sipuleucel-T was evaluated in 2 identically designed, randomized, double-blind, placebo-controlled trials (D9901 and D9902A) conducted in men with advanced prostate cancer. **METHODS:** A total of 225 patients were randomized in D9901 or D9902A to sipuleucel-T (n = 147) or placebo (n = 78), given as 3 intravenous infusions approximately 2 weeks apart. Patients were followed for survival until death or a prespecified cutoff of 36 months after randomization. **RESULTS:** In the integrated analysis of D9901 and D9902A, patients randomized to sipuleucel-T demonstrated a 33% reduction in the risk of death (hazard ratio, 1.50; 95% confidence interval, 1.10-2.05; $P = .011$; log-rank). The treatment effect remained strong after performing adjustments for imbalances in baseline prognostic factors, poststudy treatment chemotherapy use, and non–prostate cancer-related deaths. Additional support for the activity of sipuleucel-T is provided by the correlation between a measure of the product's potency, CD54 up-regulation, and overall survival. The most common adverse events associated with treatment were chills, pyrexia, headache, asthenia, dyspnea, vomiting, and tremor. These events were primarily grade 1 and 2, with durations of 1 to 2 days. **CONCLUSIONS:** The integrated results of D9901 and D9902A demonstrate a survival benefit for patients treated with sipuleucel-T compared with those treated with placebo. The generally modest toxicity profile, coupled with the survival benefit, suggests a favorable risk-benefit ratio for sipuleucel-T in patients with advanced prostate cancer. **Cancer 2009;115:3670–9. © 2009 American Cancer Society.**

KEY WORDS: prostate cancer, immunotherapy, vaccine, Provenge, sipuleucel-T, APC8015.

In the United States, prostate cancer is the most common solid tumor malignancy and the second leading cause of cancer death in men. It was expected to have accounted for 186,320 new cases and 28,660 deaths

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in the United States in 2008.[1] Although many men experience disease control after primary therapy, approximately 20% to 40% of these patients will eventually experience disease recurrence.[2] For those men whose disease recurs, typically with elevated prostate-specific antigen (PSA), androgen deprivation is commonly used and achieves temporary tumor control or regression in 80% to 85% of patients.[3-6] Despite androgen deprivation, virtually all patients will progress, and their disease will spread to distant sites, most commonly bones and/or regional lymph nodes.[7,8] Management of this castration-resistant state, also known as androgen-independent prostate cancer (AIPC), is a significant clinical challenge. Current treatment options include secondary hormone therapy, chemotherapy, and investigational agents with or without a bisphosphonate. New agents, particularly those with favorable toxicity profiles, are needed.

Sipuleucel-T, also referred to as APC8015, is an autologous active cellular immunotherapy product designed to stimulate an immune response against prostate cancer. Sipuleucel-T consists of autologous peripheral blood mononuclear cells, including antigen-presenting cells (APCs), which have been activated in vitro with a recombinant fusion protein. The recombinant fusion protein, PA2024, is composed of prostatic acid phosphatase (PAP), an antigen expressed in the majority of prostate adenocarcinomas,[9,10] linked to granulocyte-macrophage colony–stimulating factor, an immune cell activator. The processing of sipuleucel-T ex vivo has the potential benefit of achieving enhanced APC activation as a result of removing the cells from the immunosuppressive milieu of the patient, as suggested in preclinical models.[11] In phase 1 and 2 studies, sipuleucel-T appeared to be well tolerated, and PSA responses and an objective response were observed.[12-15]

The phase 3 clinical program in advanced prostate cancer included 2 identically designed randomized, double blind, placebo-controlled studies, D9901 and D9902A, intended to evaluate the safety and effectiveness of sipuleucel-T. D9901 enrolled 127 men.[16] Enrollment in D9902A was stopped at 98 patients based on initial disease progression results in D9901 and before the availability of survival results. At that time, the study was amended to become D9902B, a study in which overall survival is the primary endpoint and for which 512 patients have been enrolled. D9902B will be analyzed as an independent study, distinct from D9902A. The rationale for performing an integrated analysis of D9901 and D9902A was to provide an assessment of the treatment effect and the safety profile of sipuleucel-T in this patient population using a larger sample size. Integration of the data was justified, given that the 2 studies were identical in original design, were performed contemporaneously, had identical eligibility criteria, and had consistent treatment effect directions.

MATERIALS AND METHODS

Patients

In both D9901 and D9902A, eligible patients had histologically confirmed adenocarcinoma of the prostate with radiologic evidence of metastases, serum testosterone <50 ng/dL, and an expected survival of at least 3 months. All patients had evidence of progressive disease based on successive radiographic studies or PSA progression, as defined by PSA Consensus Criteria.[17] Other eligibility requirements included an Eastern Cooperative Oncology Group performance status of 0 or 1 and positive immunohistochemistry staining for PAP in at least 25% of tumor cells as assessed at a central laboratory. Adequate hematologic, renal, and hepatic function were required. Prior investigational agents, hormonal agents (other than luteinizing hormone–releasing hormone agonists), herbal preparations, and radiation therapy were to be discontinued at least 4 weeks before registration. Radiopharmaceuticals could not have been administered within 1 year of treatment. Concurrent bisphosphonate therapy was permitted provided therapy was initiated at least 30 days before registration and was not discontinued (or initiated) during the study. Prior chemotherapy was permitted provided at least 6 months had elapsed, or at least 3 months had elapsed and the $CD4^+$ T-cell count was $>400/\mu L$. Exclusion criteria included cancer-related bone pain, prior immunotherapy, requirement for systemic corticosteroids, requirement for opioid analgesics for cancer pain, and visceral metastases. Patients without prior bilateral orchiectomy were to be continued on gonadal suppression with a luteinizing hormone–releasing hormone agonist throughout the trial. Local institutional review boards (IRBs) approved the trials at each study center and all patients signed IRB-approved informed consent.

Trial Design and Statistical Considerations

In both D9901 and D9902A, eligible patients were randomized to either sipuleucel-T or placebo in a 2:1 ratio. Patients were stratified at randomization by bisphosphonate use (yes/no) and study center. After randomization, patients from both groups were scheduled to undergo a series of 3 leukapheresis procedures (at Weeks 0, 2, and 4), each followed 2 days later by infusion of sipuleucel-T or placebo. Patients were premedicated with acetaminophen and diphenhydramine 30 minutes before infusion. The infusions were administered over 30 minutes, and patients were observed for 30 minutes thereafter. For generation of placebo, $1/3$ of the cells collected at leukapheresis were processed similar to sipuleucel-T, but without recombinant fusion protein activation. The remaining $2/3$ of the cells were cryopreserved for potential future use in a phase 2, open-label salvage protocol (Study D9903).

Patients were monitored for disease progression by regular clinical evaluations and radiographic evaluations performed every 8 weeks until Week 32, and then every 12 weeks thereafter until disease progression. All patients were to be followed for 3 years from the time of randomization or until death, whichever occurred first.

Patients were eligible for treatment unblinding at the time of disease progression. After unblinding, patients were treated at the physician's discretion; patients in the placebo group had the option to enter Study D9903 with a product similar to sipuleucel-T, manufactured from the cells cryopreserved at the time of placebo generation. After disease progression, documentation was limited to treatment-related adverse events and survival.

The primary objective of both studies was to compare the time to disease progression in patients with asymptomatic metastatic hormone-refractory prostate cancer treated with sipuleucel-T with those treated with the control infusion. Time to disease progression was defined as the time from randomization to the time of disease progression. Disease progression included any of the following: 1) progressive disease on serial radiographic imaging tests, as determined by blinded central review; 2) new cancer-related pain associated with a radiographic anatomical correlation; or 3) other clinical events consistent with progression such as spinal cord compression, nerve root compression, or pathologic fracture. For patients with evidence of disease progression by both radiographic and other measures, the date of radiographic progression was used as the date of disease progression. PSA was not used as a measurement for progression.

Approximately 120 patients were planned for each study. A 2:1 randomization was used to increase the number of patients exposed to sipuleucel-T. Published data at the time the study was designed suggested a median time to disease progression of approximately 3 months.[18] The assumption was made that the time to disease progression for asymptomatic patients would be somewhat longer at 4 months. With a 2-sided 5% level of significance and a 2:1 patient-allocation ratio between the sipuleucel-T and placebo groups, a total of 80 events were needed in each study to achieve 80% power to detect an increase in median time to disease progression from 4 to 7.7 months (hazard ratio [HR], 1.925). Factoring in nonuniform patient entry and a loss to follow-up rate of 5%, enrollment of approximately 120 patients was targeted to achieve the required 80 events.

Overall survival was specified in both D9901 and D9902A as a planned analysis to be performed after all patients had been followed for 36 months. In D9902A, 2 patients were censored at 25.6 months and 26.7 months. To provide an additional estimate of the survival effect in this patient population, an exploratory analysis of the larger integrated dataset from D9901 and D9902A was performed.

All efficacy analyses were conducted on the intent-to-treat population, defined as all randomized patients. The log-rank test was used to evaluate time to event data for disease progression and overall survival. The hazard ratio (with a 2-sided 95% confidence interval) for the treatment effect was computed based on the unadjusted Cox regression model using the sipuleucel-T arm as the denominator. Time to event distributions were computed based on the Kaplan–Meier method. Covariate adjusted Cox regression models were used to conduct sensitivity analyses as previously described.[16] Integrated analyses were based on the same statistical method stratified by study. All tests were 2-sided.

The safety analyses were conducted on the safety population, defined as all patients who underwent at least 1 leukapheresis procedure. Two-sided *P* values associated with Fisher exact test were used for descriptive statistics to assess potential trends.

Table 1. Summary of Overall Survival and Time to Disease Progression in D9901, D9902A, and the Integrated Analysis

	D9901		D9902A		Integrated	
	Sipuleucel-T, n=82	Placebo, n=45	Sipuleucel-T, n=65	Placebo, n=33	Sipuleucel-T, n=147	Placebo, n=78
Median survival (CI), mo	25.9 (20.0-32.4)	21.4 (12.3-25.8)	19.0 (13.6-31.9)	15.7 (12.8-25.4)	23.2 (19.0-31.0)	18.9 (13.5-25.3)
Hazard ratio* (CI)	1.71 (1.13-2.58)		1.27 (0.78-2.07)		1.50 (1.10-2.05)	
Overall survival, log-rank test	P=.010		P=.331		P=.011	
Median time to progression (CI), wk	11.7 (9.1-16.6)	9.1 (8.7-13.1)	10.9 (9.3-17.7)	9.9 (8.4-18.0)	11.1 (10.0-16.3)	9.7 (8.7-13.3)
Hazard ratio* (CI)	1.45 (0.99-2.11)		1.09 (0.69-1.70)		1.26 (0.95-1.68)	
Overall TTP, log-rank test	P=.052		P=.719		P=.111	

CI indicates confidence interval; TTP, time to progression.
*The hazard ratio expresses the risk in patients treated with placebo divided by the risk for patients treated with sipuleucel-T. Therefore, a hazard ratio >1 indicates a greater risk for patients treated with placebo relative to sipuleucel-T.

RESULTS

Efficacy

In D9901, 127 patients were randomized to sipuleucel-T (n = 82) or placebo (n = 45) at 19 clinical study centers across the United States from January 2000 to October 2001. As previously described, a 31% reduction in the risk of disease progression (HR, 1.45) and a 41% reduction in the risk of death (HR, 1.71) were observed (Table 1).[16]

Enrollment in D9902A occurred from May 2000 to March 2003, and was stopped after 98 patients were randomized to sipuleucel-T (n = 65) or placebo (n = 33) at 27 clinical study centers across the United States. Several baseline factors, including PSA, alkaline phosphatase, lactate dehydrogenase (LDH), and the percentage of patients with >10 bone metastases, favored the placebo arm (Table 2). Although the HR was in favor of the sipuleucel-T arm, the time to disease progression was not statistically different between the treatment groups (HR, 1.09; 95% confidence interval [CI], 0.69-1.70; P = .72). There was a 21% reduction in the risk of death for sipuleucel-T relative to placebo, which was not statistically significant (HR, 1.27; 95%CI, 0.78-2.07; P = .33). To adjust for potential imbalances in baseline prognostic factors, a Cox multiple regression model developed from the D9901 data[16] was applied to the D9902A data. After adjusting in this model for baseline LDH (ln), PSA (ln), localization of disease, number of bone metastases, and weight (lbs), the magnitude of the survival effect for patients treated with sipuleucel-T increased (adjusted HR, 1.92; 95% CI, 1.09-3.35; P = .023).

Two hundred and twenty-five patients were randomized into the 2 studies. Twelve clinical study centers were common to both studies, and only enrolled patients on D9902A after accrual to D9901 was complete. Baseline characteristics were comparable between the 2 treatment arms (Table 2). Patient disposition is summarized in Figure 1. Of the 147 patients in the sipuleucel-T arms, 5 patients had a PSA reduction of ≥50% confirmed on a second occasion at least 4 weeks later, and an additional 2 patients had confirmed PSA reduction of ≥25%, for an overall PSA response rate of 4.8%. None of the 78 patients on the placebo arms had confirmed PSA reductions of 25% or more. The PSA response rate may be underestimated, as PSAs were only collected at baseline, Week 16, and then every 16 weeks thereafter until disease progression, and only 26% of patients had ≥2 PSA values at least 4 weeks apart. Patients randomized to sipuleucel-T had a 21% reduction in the risk of disease progression (HR, 1.26; 95% CI, 0.95-1.68; P = .111) and a 33% reduction in the risk of death (HR, 1.50; 95% CI, 1.10-2.05; P = .011) compared with patients randomized to placebo (Table 1 and Fig. 2). The median survival was 23.2 months for sipuleucel-T and 18.9 months for placebo, and the percentage of patients alive at 36 months was 33% and 15%, respectively.

Several sensitivity analyses were performed to test the robustness of the survival findings. Specifically, the treatment effect was examined in study subpopulations, adjustments were performed for baseline prognostic factors and chemotherapy use after study treatment, and prostate cancer-specific survival was determined.

The treatment effect was positive in subpopulations based on the 8 baseline prognostic factors found to be

Table 2. Baseline Characteristics

	D9901*		D9902A		Integrated	
	Sipuleucel-T, n=82	Placebo, n=45	Sipuleucel-T, n=65	Placebo, n=33	Sipuleucel-T, n=147	Placebo, n=78
Median age, y (range)	73.0 (47.0-85.0)	71.0 (50.0-86.0)	70.0 (51.0-84.0)	71.0 (57.0-87.0)	72.0 (47.0-85.0)	71.0 (50.0-87.0)
Race, white, %	89.0	93.3	90.8	93.9	89.8	93.6
ECOG status 0, %	75.6	82.2	78.5	69.7	76.9	76.9
Disease localization						
Bone only, %	42.0	23.8	47.7	30.3	44.5	26.7
Soft tissue only, %	6.2	7.1	10.8	21.2	8.2	13.3
Bone & soft tissue, %	51.9	69.0	41.5	48.5	47.3	60.0
No. bone metastases >10, %	41.5	26.7	50.8	37.5	45.5	31.2
Gleason sum 7, %	61.0	55.6	68.7	51.5	64.4	53.8
Prior chemotherapy, %	3.7	8.9	11.1	9.1	6.9	9.0
Labs, median (range)						
PSA, ng/mL	46.0 (3.5-3621)	47.9 (7.9-2799)	61.3 (8.0-936.5)	44.0 (8.2-1342.5)	50.7 (3.5-3621)	45.8 (7.9-2799)
PAP, ng/mL	7.0 (0.7-250.5)	6.5 (0.3-163.0)	4.5 (0.7-230.0)	5.1 (0.6-144.0)	6.2 (0.7-250.5)	6.3 (0.3-163.0)
Alk Phos, U/L	102.0 (42.0-1233.0)	92.0 (38.0-627.0)	140.0 (50.0-3900.0)	105.0 (34.0-923.0)	114.0 (42.0-3900.0)	95.5 (34.0-923.0)
Hemoglobin, g/dL	13.0 (8.5-16.5)	13.1 (9.3-14.8)	12.8 (9.2-15.8)	12.6 (9.0-15.3)	13.0 (8.5-16.5)	12.9 (9.0-15.3)
LDH, U/L	173.5 (119.0-533.0)	172.0 (108.0-453.0)	187.0 (101.0-1730.0)	179.0 (116.0-730.0)	183.0 (101.0-1730.0)	176.5 (108.0-730.0)

ECOG indicates Eastern Cooperative Oncology Group; PSA, prostate-specific antigen; PAP, prostatic acid phosphatase; Alk Phos, alkaline phosphatase; LDH, lactate dehydrogenase.
* Small 2006[16]; data have been updated based on additional information from clinical study centers. n represents maximum number of values for each variable.

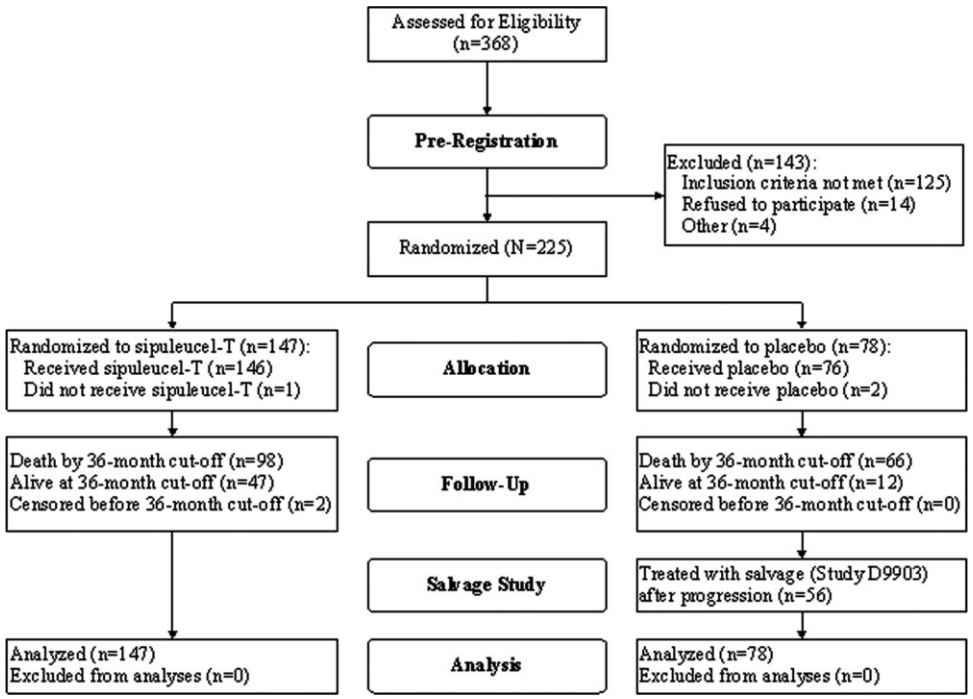

FIGURE 1. Patient disposition in integrated studies D9901 and D9902A is shown.

predictive for overall survival individually at the P .05 level (Fig. 3). In a Cox multiple regression analysis adjusting for the 5 prognostic factors previously identified as significant in a multiple variable model as described above,[16] the magnitude of the survival effect for patients treated with sipuleucel-T was maintained (HR, 1.86; 95% CI, 1.31-2.63; $P < .001$, Fig. 4).

Of the 78 patients in the placebo arm, 56 (72%) received salvage therapy with APC8015F after disease progression. The observed median time to treatment with APC8015F was 4.6 months from randomization (range, 1.8-33.5 months) and 1.7 months after disease progression (range, 0.5-14.6 months).

Similar percentages of patients in the sipuleucel-T and placebo arms received any chemotherapy after study treatment (57% vs 58%; $P = .888$), or docetaxel specifically (35% vs 40%; $P = .470$). There was no evidence of a delay in docetaxel use in the placebo arm relative to the treatment arm, and the treatment effect remained similar after adjustment for the use of docetaxel in a time-dependent covariate model (HR, 1.50; 95% CI, 1.07-2.08; Fig. 4).

To understand the influence of nonprostate cancer-specific deaths, prostate cancer-specific survival was determined. In this analysis, the 35 deaths not attributed to known or probable prostate cancer were treated as competing events. This analysis demonstrated a 42% reduction in the risk of prostate cancer-specific death (HR, 1.72; 95% CI, 1.21-2.44; $P = .002$; log-rank; Fig. 4).

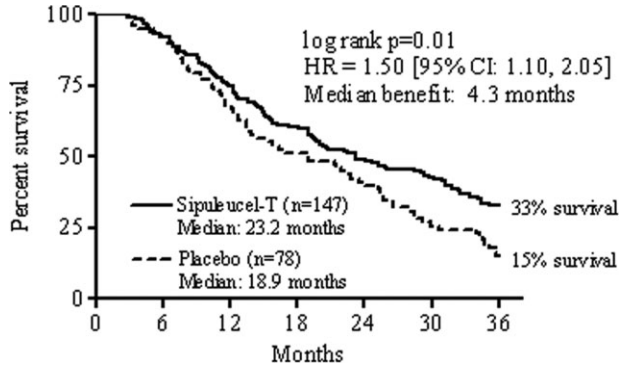

FIGURE 2. Overall patient survival (sipuleucel-T vs placebo) in integrated studies D9901 and D9902A is shown. HR indicates hazard ratio; CI, confidence interval.

Survival data for patients treated with sipuleucel-T in D9901 and D9902A were further assessed in the context of a measure of product potency, CD54 up-regulation. CD54, also known as intracellular adhesion

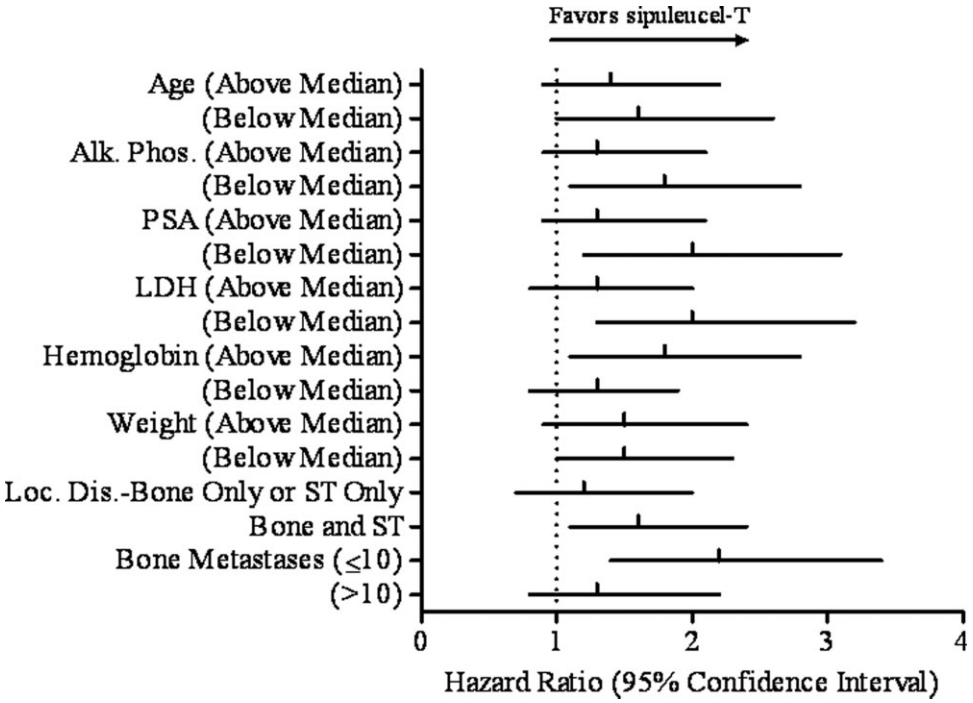

FIGURE 3. Treatment effect across subpopulations in integrated studies D9901 and D9902A is shown. Subpopulations are based on 8 baseline prognostic factors found to be predictive for overall survival. Alk. Phos. indicates alkaline phosphatase; PSA, prostate-specific antigen; LDH, lactate dehydrogenase; Loc. Dis., localization of disease; ST, soft tissue.

molecule-I, is expressed on APCs, where it plays an important role in the synapse between APCs and T cells. During the manufacture of sipuleucel-T, the number of CD54 molecules expressed on the cell surface of APCs increases as the APCs are activated. The increase in CD54 is recorded for each lot of sipuleucel-T as part of the measurement of its potency. Cumulative CD54 up-regulation ratio was calculated as the sum of Week 0, Week 2, and Week 4 final product values for each patient in the integrated dataset.

Cumulative CD54 up-regulation was used as a continuous variable in a Cox model to explore the correlation with overall survival in the sipuleucel-T treatment arm. This analysis demonstrated a strong correlation (P = .009), which persisted after adjustment for baseline prognostic factors (weight, PSA, LDH, number of bone lesions, and localization of disease; P = .022).

Safety

Integrated data from D9901 and D9902A include long-term (up to 3 years) follow-up on the 223 patients who underwent at least 1 leukapheresis. Less than 3% of patients in D9901 and D9902A were not able to receive all 3 infusions because of treatment-related adverse events.

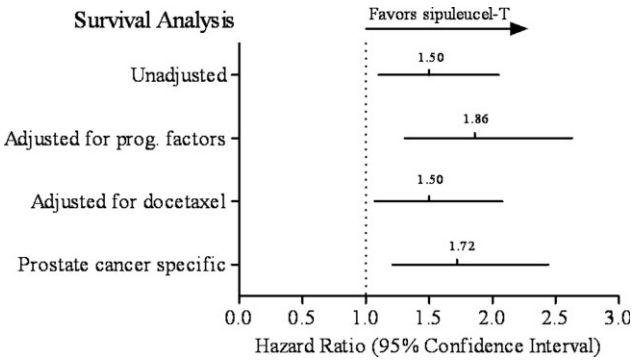

FIGURE 4. Overall survival analyses conducted for integrated studies D9901 and D9902A are summarized. prog. indicates prognostic.

The overall incidence of adverse events was similar between patients treated with sipuleucel-T (98.6%) and patients treated with placebo (96.1%). Table 3 provides a summary of adverse events occurring in ≥10% of all patients by decreasing frequency of overall occurrence. The events occurring at a higher rate (P .05) in those patients treated with sipuleucel-T compared with placebo

Table 3. Overall Incidences of Adverse Events Occurring in ≥10.0 % of Patients Treated With Sipuleucel-T by Frequency of Occurrence With Grade 3 and 4 Adverse Events, Integrated Safety Population for D9901 and D9902A

	Any Grade*		Grade 3 or 4*	
Preferred Term	Sipuleucel-T, n=147, No. (%)	Placebo, n=76, No. (%)	Sipuleucel-T, n=147, No. (%)	Placebo, n=76, No. (%)
Any adverse event	145 (98.6)	73 (96.1)	49 (33.3)	21 (27.6)
Chills	85 (57.8)	6 (7.9)	7 (4.8)	0 (0.0)
Fatigue	63 (42.9)	22 (28.9)	2 (1.4)	0 (0.0)
Pyrexia	47 (32.0)	5 (6.6)	3 (2.0)	0 (0.0)
Back pain	33 (22.4)	18 (23.7)	4 (2.7)	1 (1.3)
Headache	28 (19.0)	5 (6.6)	2 (1.4)	0 (0.0)
Arthralgia	22 (15.0)	14 (18.4)	3 (2.0)	0 (0.0)
Asthenia	21 (14.3)	3 (3.9)	0 (0.0)	0 (0.0)
Nausea	21 (14.3)	6 (7.9)	1 (0.7)	0 (0.0)
Anemia	20 (13.6)	8 (10.5)	6 (4.1)†	0 (0.0)
Paresthesia	19 (12.9)	7 (9.2)	0 (0.0)	0 (0.0)
Chest wall pain	16 (10.9)	5 (6.6)	3 (2.0)	0 (0.0)
Dyspnea	16 (10.9)	2 (2.6)	5 (3.4)	1 (1.3)
Vomiting	16 (10.9)	2 (2.6)	1 (0.7)	0 (0.0)

Randomization at study entry was 2:1 for sipuleucel-T:placebo. Two patients randomized to placebo did not undergo a leukapheresis procedure and are not included in the safety population.
* Severity grade was assessed using the National Cancer Institute's Common Toxicity Criteria (version 2.0).
† All 6 cases of anemia were grade 3.

were chills, pyrexia, headache, asthenia, dyspnea, vomiting, and tremor. These adverse reactions were primarily grade 1 and 2, with a duration of 1 to 2 days. There were no grade 3 or 4 adverse events reported in ≥5% of patients in either treatment arm, and there were no significant differences in the incidence of grade 3 or 4 adverse events occurring between the treatment arms.

The frequency of serious adverse events was similar between the patients treated with sipuleucel-T and placebo (23.8% vs 22.4%, respectively). For serious and grade 3 or 4 adverse events that were considered infusion-related, the majority of events were 24 hours in duration, and all patients recovered.

A possible increased risk of cerebrovascular events was observed in the sipuleucel-T treatment arm. All types of cerebrovascular events (eg, hemorrhagic, ischemic, embolic, transient ischemic attack, and bleeding from a dural metastatic lesion) were included in these analyses. The incidence of cerebrovascular events reported as adverse events or as causes of death was 7.5% (11 of 147) in the treatment arm and 2.6% (2 of 76) in the placebo arm. Accounting for the length of time since randomization for each patient, the number of events per 100 patient-years of follow-up was 3.99 (95% CI, 1.99-7.14) in the treatment arm compared with 1.58 in the placebo arm (95% CI, 0.19-5.69). There have been no cerebrovascular events reported in subjects after salvage therapy in Study D9903; when follow-up time after salvage treatment is included in the treatment group rather than the placebo group, the incidence was 3.18 per 100 patient-years of follow-up (95% CI, 1.59-5.69) in the treatment group compared with 3.53 in the placebo group (95% CI, 0.43-12.77). The cerebrovascular events in the treatment arm were reported over a wide range of time (median time from first infusion: 167 days; range, 26-859 days), and the majority of events were nonfatal.

DISCUSSION

In a randomized phase 3 study, D9901, sipuleucel-T treatment has previously been shown to provide a survival benefit as well as a trend toward a delay in time to disease progression in men with metastatic AIPC. A second randomized phase 3 study, D9902A, demonstrated a trend toward improved overall survival. The lack of statistical significance and a smaller observed treatment effect for overall survival in D9902A may have been in part attributable to the smaller sample size; the trial was stopped early and resulted in 26% fewer death events than D9901. In addition, baseline prognostic factors in D9902A were

less well balanced than in D9901. After adjustment for baseline prognostic factors, the survival treatment effect in D9902A was comparable to that observed in D9901.

To provide an estimate of the overall sipuleucel-T treatment effect in this patient population, we performed an integrated analysis of D9901 and D9902A. This analysis allowed us to include all patients from both randomized studies in AIPC with identical eligibility criteria as well as incorporate potential study to study variability.

In the integrated analysis of D9901 and D9902A, we observed a trend toward a delay in the time to disease progression. The rapid rate of disease progression in these studies likely made it more challenging to demonstrate an effect on the disease progression endpoint. At the time D9901 and D9902A were designed, it was anticipated that the target population of patients with asymptomatic, metastatic AIPC would progress more slowly than patients with symptomatic disease, thereby allowing more time for the immunotherapy to take effect. This assumption proved incorrect, with the median time to disease progression being comparable to that observed in symptomatic patients,[16] a finding subsequently substantiated in studies of atrasentan[19] and zoledronic acid.[20] With median time to progression of 10-12 weeks in D9901 and D9902A, many patients had progressed by the time of the first scan, scheduled at 8 weeks, such that patients may have reached the progression endpoint before achieving the maximal immune response to therapy. We have previously demonstrated that maximal immune response in some patients may not occur until 12 weeks or longer after initiation of therapy.[12] Progression as defined in this study may therefore have reflected in part what was in progress at the time of enrollment, and not necessarily progression on therapy. For this reason, time to progression may not be an appropriate endpoint when testing the effect of immunotherapy in this patient population. Studies of other biologic agents also suggest that there may not be a strong correlation between disease progression and overall survival.[21,22]

Overall survival may be a more appropriate endpoint for advanced prostate cancer trials, because death events generally occur much later than progression events, allowing more time for the therapy to take effect, particularly for immunotherapeutic agents such as sipuleucel-T. The 33% reduction in the risk of death, the 4.3-month median survival difference, and the >100% increase in the 36-month overall survival rate of men treated with sipuleucel-T compared with placebo demonstrate the potential clinical significance of the treatment effect. The treatment effect was observed despite the presence of a crossover trial design, in which 72% of patients randomized to placebo received salvage therapy with a version of sipuleucel-T made from cells cryopreserved at the time of placebo manufacture. Importantly, the survival benefit remained strong after adjusting for baseline prognostic factors in a multiple regression model. Additional analyses suggest that the survival benefit cannot be explained by an imbalance in the timing or use of chemotherapy after study treatment, or by an imbalance in nonprostate cancer-related deaths.

The survival differences observed in D9901 and D9902A occurred in the setting of approximately 60% of patients going on to receive chemotherapy after study treatment. These data would support the use of sipuleucel-T before the initiation of chemotherapy, but additional studies are required to determine the optimal sequencing of sipuleucel-T and chemotherapy.

There was a positive correlation between greater cumulative CD54 up-regulation, a measure of the product potency, and a reduction in the risk of death. The correlation remained strong after adjusting for important baseline prognostic factors, suggesting that the prognostic significance of the degree of CD54 up-regulation is independent of other baseline prognostic factors. These analyses support the hypothesis that sipuleucel-T is engaging the immune system.

The adverse events associated with sipuleucel-T generally occur soon after treatment, are low grade, and are transient, as previously described.[16] Conclusions regarding the possible increased risk of cerebrovascular events cannot be drawn at this time, given the small number of events and the large confidence intervals. An ongoing study in androgen-dependent disease has demonstrated a trend in the opposite direction, with more cerebrovascular events occurring in the placebo arm.[23] Additional studies are underway to better characterize the nature of these events.

In conclusion, the results of D9901 and D9902A suggest that sipuleucel-T may prolong overall survival. These results are supported by several robustness analyses. The generally modest toxicity profile, coupled with the survival benefit, suggests a favorable risk-benefit ratio for

sipuleucel-T in patients with asymptomatic, metastatic AIPC. An additional randomized phase 3 trial in this patient population is ongoing.

Conflict of Interest Disclosures

This trial was supported by Dendreon Corporation.

Paul F. Schellhammer owns stock in Dendreon Corporation.

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Nicole Provost is an employee of and owns stock in Dendreon Corporation.

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