VOLUME 24 · NUMBER 19 · JULY 1 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Placebo-Controlled Phase III Trial of Immunologic Therapy with Sipuleucel-T (APC8015) in Patients with Metastatic, Asymptomatic Hormone Refractory Prostate Cancer

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Submitted October 7, 2005; accepted April 19, 2006.

Supported by the Dendreon Corporation.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/06/2419-3089/$20.00

DOI: 10.1200/JCO.2005.04.5252

ABSTRACT

Purpose
Sipuleucel-T (APC8015) is an investigational immunotherapy product designed to stimulate T-cell immunity against prostatic acid phosphatase. A phase III study was undertaken to evaluate the safety and efficacy of sipuleucel-T in a placebo-controlled study.

Patients and Methods
A total of 127 patients with asymptomatic metastatic hormone refractory prostate cancer (HRPC) were randomly assigned in a 2:1 ratio to receive three infusions of sipuleucel-T (n = 82) or placebo (n = 45) every 2 weeks. On disease progression, placebo patients could receive APC8015F, a product made with frozen leukapheresis cells.

Results
Of the 127 patients, 115 patients had progressive disease at the time of data analysis, and all patients were followed for survival for 36 months. The median for time to disease progression (TTP) for sipuleucel-T was 11.7 weeks compared with 10.0 weeks for placebo ($P = .052$, log-rank; hazard ratio [HR], 1.45; 95% CI, 0.99 to 2.11). Median survival was 25.9 months for sipuleucel-T and 21.4 months for placebo ($P = .01$, log-rank; HR, 1.70; 95% CI, 1.13 to 2.56). Treatment remained a strong independent predictor of overall survival after adjusting for prognostic factors using a Cox multivariable regression model ($P = .002$, Wald test; HR, 2.12; 95% CI, 1.31 to 3.44). The median ratio of T-cell stimulation at 8 weeks to pretreatment was eight-fold higher in sipuleucel-T-treated patients (16.9 *v* 1.99; $P < .001$). Sipuleucel-T therapy was well tolerated.

Conclusion
While the improvement in the primary end point TTP did not achieve statistical significance, this study suggests that sipuleucel-T may provide a survival advantage to asymptomatic HRPC patients. Supportive studies are underway.

J Clin Oncol 24:3089-3094. © 2006 by American Society of Clinical Oncology

INTRODUCTION

Prostate cancer is the most common malignancy in men, accounting for approximately 30,350 deaths in the United States in 2005.[1] Approximately 15% of men with prostate cancer present with metastatic disease, and 20% to 30% of men with localized disease treated with definitive local therapy subsequently develop metastatic disease. While the vast majority of patients with metastatic disease demonstrate a transient response to androgen deprivation, eventually all patients develop hormone refractory prostate cancer (HRPC) and virtually all prostate cancer deaths are due to the development of metastatic HRPC.[2] While docetaxel-based chemotherapy regimens have shown a modest survival advantage in HRPC patients, median survival remains approximately 19 months,[3,4] and not all patients are candidates for chemotherapy. Novel agents and approaches are needed. One such approach involves the stimulation of prostate cancer specific T-cell immune responses.

Sipuleucel-T is an investigational immunotherapy product designed to stimulate T-cell immunity to prostatic acid phosphatase (PAP), an antigen expressed in the vast majority of prostate cancers but not in nonprostate tissue. Specifically, sipuleucel-T is composed of autologous antigen presenting cells (APCs) cultured with a fusion protein, termed PA2024, which consists of PAP linked to granulocyte-macrophage colony-stimulating factor.[5-7] PA2024 provides efficient loading and processing of antigen by APCs.[8] Data from phase I and II trials suggest that quiescent APCs cultured with PA2024 undergo activation and upregulation of costimulatory molecules.[5]

Phase I and II trials demonstrated prostate-specific antigen (PSA) declines of more than 50% in approximately 10% of patients, as well as one striking objective response. Of interest, those patients who developed an immune response to native PAP had a longer time to disease progression (TTP; 34 weeks *v* 13 weeks; $P = .03$).[5] Treatment was well tolerated, with no dose-limiting toxicities observed. Based on these data, a double-blind, placebo-controlled, randomized phase III trial was designed to test the effect of sipuleucel-T on TTP and survival in patients with asymptomatic metastatic HRPC.

PATIENTS AND METHODS

Patients

This study involved 19 centers in the United States. Eligible patients had histologically confirmed adenocarcinoma of the prostate with radiologic evidence of metastases, serum testosterone less than 50 ng/dL, and an expected survival of at least 3 months. All patients had evidence of progressive disease, as defined by PSA Consensus Criteria.[9] 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 cells assessed at a central laboratory. Negative serologic tests for human immunodeficiency virus, human T-cell leukemia virus type 1, hepatitis B, and hepatitis C were required, as were adequate hematologic, renal, and hepatic function. Prior investigational agents, other hormones, Saw Palmetto, PC-SPES, or other herbal preparations were allowed provided they were discontinued at least 1 month before 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 radiation therapy must have been completed at least 1 month before treatment, and radiopharmaceuticals could not have been administered within 1 year of treatment. Patients who required concurrent systemic corticosteroids or those who received prior immunotherapy were not eligible. Patients without prior bilateral orchiectomy continued on gonadal suppression with a luteinizing hormone-releasing hormone agonist throughout the trial. 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 greater than 400. Patients with cancer-related bone pain, or the requirement of opioid analgesics for cancer pain, as well as patients with visceral metastases were not eligible. Local institutional review boards approved the trial at each study center and all patients signed institutional review board approved informed consent.

Random Assignment and Treatment

A centrally administered, block random assignment method encompassing all study centers was employed to assign patients to treatment in a 2:1 ratio (sipuleucel-T: placebo). Treatment was given on weeks 0, 2, and 4. Sipuleucel-T and placebo were prepared fresh for each treatment. Stratification variables were study center and bisphosphonate use (yes/no). Patients underwent a standard 1.5 to 2.0 blood volume mononuclear cell leukapheresis, which was transported to a sponsor-designated manufacturing facility. APCs were isolated from the leukapheresis product and sipuleucel-T was prepared as previously described.[5,6] The time from apheresis to infusion of final product was approximately 48 hours. For patients randomly assigned to placebo, APCs were similarly prepared and divided into two aliquots. One third of the cells were reinfused without being pulsed with PA2024, serving as placebo. The remaining two thirds were cryopreserved to later generate the open-label product, APC8015F. (Patients were unblinded at the time of disease progression and those randomly assigned to placebo were eligible for treatment with APC8015F.) For each of the three sipuleucel-T infusions, the number of cells infused was the maximum number of cells that could be prepared from the leukapheresis product; the median number of nucleated cells per infusion was 3.65×10^9 and the median number of CD54+ bright cells per infusion was 7.45×10^8. Patients were premedicated 30 minutes before each infusion with acetaminophen (650 mg) and diphenhydramine (50 mg). Sipuleucel-T or placebo was administered intravenously over 30 minutes, and patients were observed for 30 minutes after each infusion. After treatment, patients were observed every 8 to 12 weeks for safety (physical examinations, adverse event assessments, laboratory tests) and progression (radiographic imaging studies and pain assessment) until disease progression, at which point a crossover to open-label APC8015F was available for patients treated with placebo.

Immunologic Testing

T-cell proliferation response to sipuleucel-T was evaluated in those patients for whom samples were submitted at baseline (preinfusion) and at week 8 (postinfusion) and for whom the samples could be processed within 24 hours of collection. All immunologic assays were undertaken without the knowledge of treatment assignment. Peripheral blood mononuclear cells (PBMCs) were isolated from peripheral blood using CPT tubes. The T-cell proliferation assay was set up in triplicate in 96-well round-bottom plates with PBMCs acting as both APCs and responding cells. PA2024 was used at a concentration of 50 μg/mL, while PBMCs without antigen were used as the negative control. Cells were incubated for 6 days, and [^{3}H]thymidine was added for the final 18 hours to assess T-cell proliferation. Plates were harvested onto filter mats and radioactivity was measured by a scintillation counter. Data were reported as counts per minute (cpm). For each assay, the T-cell stimulation index was defined as median cpm with antigen/median cpm without antigen.

Statistical Considerations/Trial End Points

Data from a small phase II study of sipuleucel-T demonstrated a trend in delaying TTP correlating with T-cell immune response to PAP.[5] Because of the confounding nature of subsequent treatments, including crossover to open-label APC8015F, TTP was chosen as a primary end point and was defined by any of the following: progressive disease on serial radiographic imaging tests; new cancer-related pain associated with a radiographic anatomic correlation or; other clinical events consistent with progression such as spinal cord compression, nerve root compression, or pathologic fracture. Radiographic imaging studies were specified in the protocol to occur every 8 weeks until week 32 then every 12 weeks thereafter, and progression was confirmed by central review of scans. PSA was not used to determine disease progression or to trigger radiographic evaluations. Progressive disease was defined as an increase greater than 50% in measurable disease, clear worsening of nonmeasurable disease, the appearance of at least two new lesions on a bone scan, the development of cancer-related pain that correlated with a site of metastasis, or the development of other clinical events consistent with progression (such as spinal cord compression or pathologic fracture).

Published data suggest that the median TTP in patients with symptomatic HRPC is approximately 3 months.[10] The assumption was made that the TTP for asymptomatic patients would be somewhat longer (4 months; null hypothesis). Sample size calculations were based on attaining a power of 80% with a two sided .05 significance level and the assumption that sipuleucel-T would result in an increase in median TTP to 7.7 months, translating into a hazard ratio (HR) of 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.

While this study was not powered to detect a survival difference between the two treatment arms, there was a protocol-specified requirement to follow each patient for survival (and treatment-related adverse events) up to 36 months after random assignment. The median TTP and survival time were estimated with the Kaplan-Meier method.[11]

The log-rank test was performed to compare distributions of TTP and survival times. All tests were two sided and performed at the .05 level. Risk ratios with 95% CIs based on the Cox proportional hazards model were also provided. For the analysis of T-cell proliferative responses, the ratio of stimulation index at 8 weeks was compared with the ratio of stimulation index at baseline for different subsets using the Wilcoxon rank sum method.[12]

To test the robustness of the survival findings, the individual effect of 20 potentially important prognostic factors that have been described in the literature was evaluated. Using exploratory Cox regression models, each one having treatment and a single covariate as main effects, the treatment effect

remained significant. Covariates that were significant at the .05 level were then selected to build a predictive multicovariate Cox regression survival model. A backwards stepwise selection method ($P = .05$ for entry and $P = .10$ for removal, likelihood ratio test) was used to identify significant prognostic factors and their impact on treatment effect.

RESULTS

Characteristics of the Patients

Between January 2000 and October 2001, 127 patients were enrolled at 19 study centers. Eighty-two patients were randomly assigned to receive sipuleucel-T; 45 patients were randomly assigned to receive placebo. Table 1 demonstrates that the treatment groups were similar with regard to median age, race, Eastern Cooperative Oncology Group performance status, PSA, PAP, alkaline phosphatase, hemoglobin, lactate dehydrogenase, and Gleason score. While not statistically significant, there were apparent differences in the treatment arms with respect to bone only disease (42.7% in sipuleucel-T *v* 26.7% in placebo) and the percentage of patients with more than 10 bone metastases (40.2% in sipuleucel-T *v* 26.7 in placebo). Overall, however, bone involvement was similar (93.9% in sipuleucel-T arm and 91.3% in the placebo arm.). All 127 patients received at least one infusion, and all are included in the intent-to-treat (ITT) population.

Table 1. Patient Characteristics

Characteristic	Sipuleucel-T (n = 82) No.	%	Placebo (n = 45) No.	%
Age, years				
Median	73.0		71.0	
Range	47-85		50-86	
Race: white	73	89.0	42	93.3
Bisphosphonate use at entry				
No	29	96.3	42	93.3
Yes	3	3.7	3	6.7
Disease location				
Bone only	35	42.7	12	26.7
Soft tissue only	5	6.1	4	8.9
Bone and soft tissue	42	51.2	29	64.4
Number of bone mets				
1-10	44	53.6	29	64.5
> 10	33	40.2	12	26.7
ECOG performance status				
0	62	75.6	37	82.2
1	20	24.4	8	17.8
Median PSA, ng/mL	46.0		47.9	
Range	3.5-3,621		7.9-2,799	
Median PAP, ng/mL	7.0		6.5	
Range	0.7-250.5		0.3-163.0	
Median alkaline phosphatase,U/L	102.0		92.0	
Range	42-1,233		38-627	
Median hemoglobin, g/dL	13.0		13.1	
Range	8.5-16.5		9.3-14.8	
Median LDH, U/L	173.5		172.0	
Range	119-533		108-453	
Gleason Score				
Median	7		7	
≤ 7	50	61.0	25	55.6
8	32	39.0	20	44.4
Patients with prior chemotherapy	3	3.7	4	8.9
Patients receiving docetaxel-based chemotherapy subsequent to study treatment	28	35.9	20	47.6

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen; PAP, prostatic acid phosphatase; LDH, lactate dehydrogenase.

Patient Disposition

Disposition specifics are presented in Figure 1. Treatment with chemotherapy or other anticancer therapy was prohibited until the primary end point of TTP was met. After progression, 55.7% of sipuleucel-T patients and 62.8% of placebo patients received some form of chemotherapy, 43.6% of sipuleucel-T and 52.4% of placebo patients received a taxane-based chemotherapy, and 35.9% of sipuleucel-T and 47.6% of placebo patients received docetaxel-based therapy (Table 1).

Clinical Results

A total of 115 patients (90.5%) contributed a progression event to the primary analysis of TTP (Fig 1). All patients except one progressed before death. The one exception was a man treated with sipuleucel-T who developed and succumbed to complications of a glioblastoma 6 months after treatment. The median TTP was 11.7 weeks (95% CI, 9.1 to 16.6) in sipuleucel-T-treated patients and 10.0 weeks (95% CI, 8.7 to 13.1) in placebo-treated patients ($P = .052$, log-rank; HR, 1.45; 95% CI, 0.99 to 2.11; Fig 2.)

Complete follow-up to death or to the prespecified 36 month end point after random assignment was obtained for all 127 patients. In an ITT analysis, the median overall survival was 25.9 months (95% CI, 20.0 to 31.9) in sipuleucel-T-treated patients compared with 21.4 months (95% CI, 12.3 to 25.8) in placebo-treated patients ($P = .01$, log-rank; HR, 1.70; 95% CI, 1.13 to 2.56; Fig 3.) The estimated survival rate at the last assessment before censoring at 36 months was 34% in the sipuleucel-T group compared with 11% in the placebo group ($P = .005$, χ^2 based on the number of survivors at 36 months). The placebo group for these analyses included the 34 patients (75.5%) subsequently treated with open-label APC8015F.

While overall survival at 36 months was prespecified in the analysis plan, it was not specified as the primary efficacy end point, so the *P* value obtained for this analysis should be interpreted with caution. Therefore, in order to assess the robustness of the survival benefit observed, an exploratory Cox regression analysis identified five clinical variables (lactate dehydrogenase, PSA, number of bone metastases, body weight, and localization of disease) that were highly predictive of overall survival in this study cohort (supra vide). To correct for any potential imbalances, the treatment effect of sipuleucel-T was adjusted using these variables and remained statistically significant ($P < .002$, Wald test; HR, 2.12; 95% CI, 1.31 to 3.44).

Immune Monitoring

Adequate sample collection for immunologic testing was available for 49 patients: 18 treated with placebo (40% of total); 31 treated with sipuleucel-T (38% of total). The PA2024 T-cell stimulation index is a measure of specific T-cell responsiveness against the target antigen. This exploratory analysis was performed in a subset of patients for whom cells could be processed within 24 hours of collection, thus precluding the need to freeze the cells before analysis. All analyses were performed before study unblinding. The median ratio of the T-cell

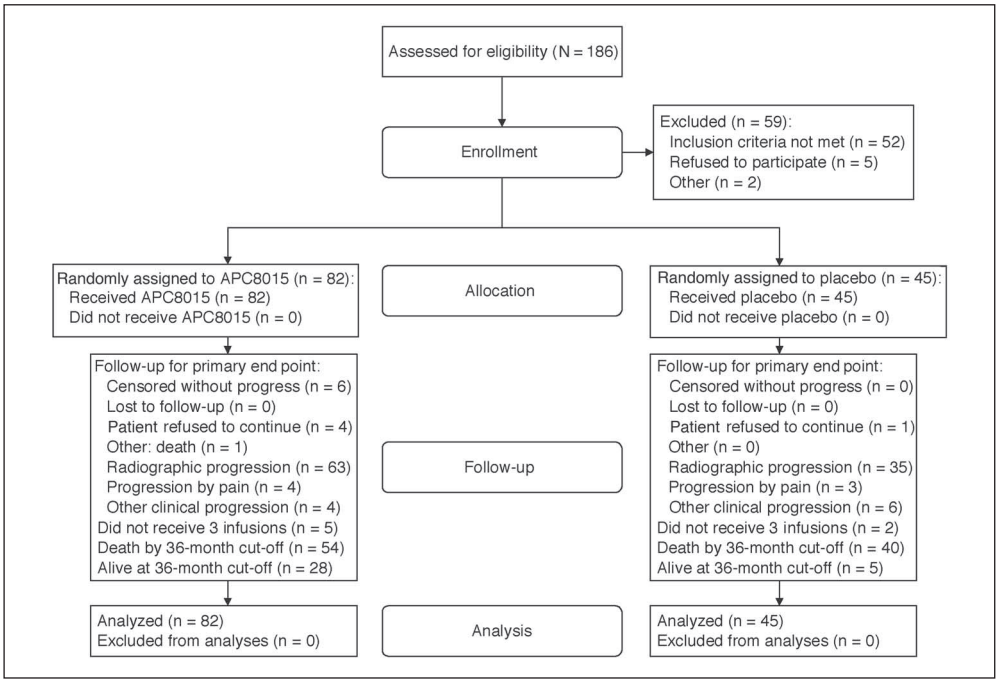

Fig 1. Patient disposition.

stimulation index at 8 weeks versus baseline (preinfusion) was approximately eight-fold higher in sipuleucel-T- versus placebo-treated patients (16.91 Wilcoxon *v* 1.99; Wilcoxon rank sum $P < .001$).

Toxicity

Therapy was generally well tolerated. Toxicities that were significantly more common ($P \leq .05$) in sipuleucel-T treated patients included rigors (59.8% *v* 8.9%), pyrexia (29.3% *v* 2.2%), tremor (9.8% *v* 0%), and feeling cold (8.5% *v* 0%; Table 2.) Rigors and pyrexia were seen primarily as infusion reactions. The majority of toxicities from each treatment group (70.7% in sipuleucel-T; 68.9% in placebo) were grade 1 or 2. Ninety-five percent of patients received all three planned infusions. No patient discontinued the trial because of toxicity.

DISCUSSION

This phase III trial did not demonstrate an improvement in the primary end point (TTP) in asymptomatic metastatic HRPC patients treated with sipuleucel-T compared with placebo. Nevertheless, in an ITT analysis, the use of sipuleucel-T demonstrated a 4.5-month improvement in overall survival, which achieved statistical significance ($P = .01$). This is a mature study, with 91% of patients having reached the primary end point at the time of analysis and 100% of patients assessed for survival. At 36 months, the estimated survival rate in the sipuleucel-T group was 34% compared with 11% in the placebo group. The treatment groups appeared to be balanced regarding predictive risk features,[13,14] and treatment remained a strong independent predictor of overall survival after adjustment for prognostic factors in a multivariable model. In addition, an analysis of chemotherapy use after protocol treatment revealed no difference in the percentage of patients in either group who received docetaxel, the only chemotherapy that has shown a significant survival benefit in this population. Despite the similarities between the two cohorts, it is possible that the difference in survival could be explained by an imbalance in a yet to be identified prognostic factor in the setting of a small sample size.

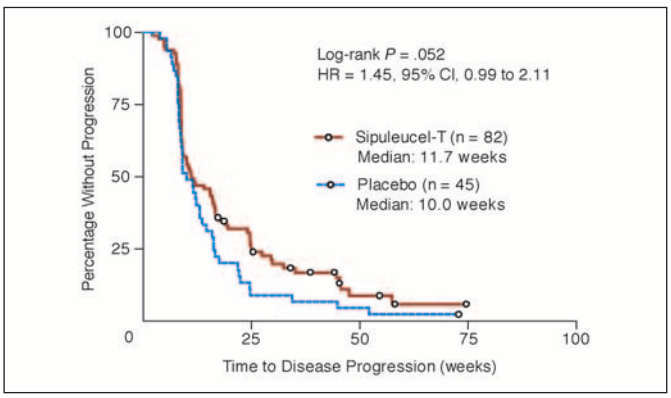

Fig 2. Primary end point, time to disease progression (intent-to-treat population). HR, hazard ratio.

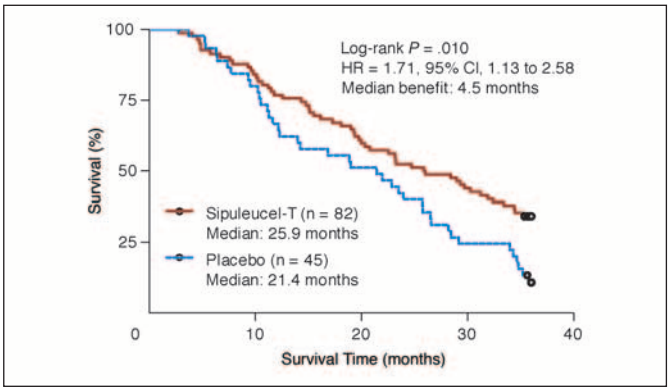

Fig 3. Final overall survival (intent-to-treat population). HR, hazard ratio.

Table 2. AEs Occurring in 10% of Patients in Either Treatment Group by Overall Incidence and NCI Toxicity Grade and AEs With Differences ($P \leq .05$) in Incidence Between Treatment Groups

	Total (n = 127)				Grade 1 and 2				Grade 3 and 4			
	Sipuleucel-T (n = 82)		Placebo (n = 45)		Sipuleucel-T (n = 82)		Placebo (n = 45)		Sipuleucel-T (n = 82)		Placebo (n = 45)	
Type	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Any AE	78	95.1	42	93.3	58	70.8	31	68.9	20	24.4	11	24.4
Rigors	49	59.8	4	8.9	45	54.9	4	8.9	4	4.9	0	0.0
Fatigue	32	39.0	14	31.1	31	37.8	13	28.9	1	1.2	1	2.2
Pyrexia	24	29.3	1	2.2	22	26.8	1	2.2	2	2.4	0	0.0
Back pain	14	17.1	9	20.0	12	14.6	9	20.0	2	2.4	0	0.0
Arthralgia	13	15.9	3	6.7	12	14.6	3	6.7	1	1.2	0	0.0
Nausea	10	12.2	5	11.1	10	12.2	5	11.1	0	0.0	0	0.0
Dyspnea	12	14.6	2	4.4	8	9.8	1	2.2	4	4.9	1	2.2
Headache	12	14.6	2	4.4	12	14.6	2	4.4	0	0.0	0	0.0
Parasthesia	12	14.6	2	4.4	12	14.6	2	4.4	0	0.0	0	0.0
Anemia	7	8.5	6	13.3	5	6.1	6	13.3	2	2.4	0	0.0
Constipation	7	8.5	6	13.3	6	7.3	5	11.1	1	1.2	1	2.2
Pain in extremities	5	6.1	6	13.3	4	4.9	6	13.3	1	1.2	0	0.0
Edema peripheral	5	6.1	5	11.1	5	6.1	5	11.1	0	0.0	0	
Vomiting	9	11.0	1	2.2	9	11.0	1	2.2	0	0.0	0	0.0
Diarrhea	4	4.9	5	11.1	4	4.9	5	11.1	0	0.0	0	0.0
Tremor	8	9.8	0	0.0	8	9.8	0	0.0	0	0.0	0	0.0
Feeling cold	7	8.5	0	0.0	7	8.5	0	0.0	0	0.0	0	0.0

Abbreviation: AE, adverse event; NCI, National Cancer Institute.
$P \leq .05$ versus placebo, all grades.

While this study was only powered for a large impact on TTP, the difference in the effect of sipuleucel-T on TTP and overall survival illustrates the difficulties of using TTP as an intermediate marker for overall survival in HRPC patients treated with immunotherapy. Examination of the Kaplan-Meier curves demonstrates a rapid decline in the cumulative proportion remaining progression free within the first 2 months, at which point the curves begin to separate. Phase II studies have suggested that maximum T-cell reactivity takes 8 to 10 weeks to achieve,[5] so some patients may have developed progressive disease before the treatment achieved its biologic effects.

In symptomatic HRPC patients, the median TTP has been reported to be about 3 months.[10] However, there exist relatively few data sets describing TTP in HRPC patients who are asymptomatic. It has generally been assumed that TTP is considerably longer in asymptomatic patients compared with patients with pain, making this an attractive cohort of patients in which to study the effects of novel therapeutic agents. A longer progression-free period presumably would provide a longer period of time for novel agents, some of which may be cytostatic, to exert a biologic effect. However, the results from the placebo group in this trial suggest that this assumption may be incorrect, as the median TTP was quite short at 10 weeks. Similar results have been reported in another series of patients with asymptomatic HRPC, with a median TTP of about 12 weeks.[15] It is therefore possible that other clinical features apart from the presence of symptoms carry more weight with regards to predicting TTP. The rapid development of progression may make TTP an unsuitable intermediate marker of survival when the putative biologic effects of the investigational agent tend to occur after progression. An immunotherapeutic approach such as sipuleucel-T may therefore have more gradual antitumor effects that will be more apparent in patients with less aggressive disease.

The median survival of sipuleucel-T-treated patients was 25.9 months versus 21.4 months for placebo-treated patients. In contrast, two randomized trials of mitoxantrone versus docetaxel demonstrated survival times of 18.9 months and 17.5 months in docetaxel-treated patients, and 16.5 months and 15.6 months in mitoxantrone-treated patients, respectively.[3,4] While there is an overlap in the 95% CIs of these values, these data suggest that the present study included a group of patients with a somewhat better prognosis.

Treatment options for patients with metastatic HRPC are limited and the development of novel therapies with acceptable toxicity and safety profiles is important. In this study, no patients were removed from the trial for toxicity, there were no treatment-related deaths, and grade 3 and 4 toxicities were rare. While 24.4% of both sipuleucel-T and placebo patients experienced a grade 3 or 4 toxicity, no single grade 3 or 4 toxicity occurred in more than 6% of patients.

In summary, this study suggests that while sipuleucel-T fell short ($P = .052$) of demonstrating a statistically significant difference in TTP, it may provide a survival advantage to asymptomatic HRPC patients. Supportive studies are underway to confirm this effect.

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Acknowledgment

We are indebted to the investigators, in addition to the authors, who participated in this trial, to Amy Myers for her writing and editing assistance, to Vivian Weinberg, PhD, for her statistical review, and to Jelle Kylstra, MD, for his contributions during the trial.

Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Authors	Employment	Leadership	Consultant	Stock	Honoraria	Research Funds	Testimony	Other
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Dollar Amount Codes (A) < $10,000 (B) $10,000-99,999 (C) $100,000 (N/R) Not Required

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Other: Celestia S. Higano, Charles H. Redfern, John J. Nemunaitis, Frank H. Valone [Critical content review of manuscript]