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Sipuleucel-T Immunotherapy for Castration-Resistant Prostate Cancer

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ABSTRACT

BACKGROUND

Sipuleucel-T, an autologous active cellular immunotherapy, has shown evidence of efficacy in reducing the risk of death among men with metastatic castration-resistant prostate cancer.

METHODS

In this double-blind, placebo-controlled, multicenter phase 3 trial, we randomly assigned 512 patients in a 2:1 ratio to receive either sipuleucel-T (341 patients) or placebo (171 patients) administered intravenously every 2 weeks, for a total of three infusions. The primary end point was overall survival, analyzed by means of a stratified Cox regression model adjusted for baseline levels of serum prostate-specific antigen (PSA) and lactate dehydrogenase.

RESULTS

In the sipuleucel-T group, there was a relative reduction of 22% in the risk of death as compared with the placebo group (hazard ratio, 0.78; 95% confidence interval [CI], 0.61 to 0.98; P=0.03). This reduction represented a 4.1-month improvement in median survival (25.8 months in the sipuleucel-T group vs. 21.7 months in the placebo group). The 36-month survival probability was 31.7% in the sipuleucel-T group versus 23.0% in the placebo group. The treatment effect was also observed with the use of an unadjusted Cox model and a log-rank test (hazard ratio, 0.77; 95% CI, 0.61 to 0.97; P=0.02) and after adjustment for use of docetaxel after the study therapy (hazard ratio, 0.78; 95% CI, 0.62 to 0.98; P=0.03). The time to objective disease progression was similar in the two study groups. Immune responses to the immunizing antigen were observed in patients who received sipuleucel-T. Adverse events that were more frequently reported in the sipuleucel-T group than in the placebo group included chills, fever, and headache.

CONCLUSIONS

The use of sipuleucel-T prolonged overall survival among men with metastatic castration-resistant prostate cancer. No effect on the time to disease progression was observed. (Funded by Dendreon; ClinicalTrials.gov number, NCT00065442.)

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Prostate cancer is the most common noncutaneous cancer among men in the United States and is the second leading cause of death from cancer in men.[1] Localized prostate cancer may be cured with surgery or radiation therapy, but the disease recurs in approximately 20 to 30% of patients. Androgen-deprivation therapy, the most common treatment after recurrence, is effective, but the disease eventually progresses in most patients who receive such treatment.[2] For men with metastatic castration-resistant prostate cancer, the median survival in recent phase 3 studies has ranged from 12.2 to 21.7 months.[3-9] A chemotherapeutic agent, docetaxel, is the only approved therapy that has been shown to prolong survival among men with this condition, conferring a median survival benefit of 2 to 3 months, as compared with mitoxantrone and prednisone.[8-10] Combination therapy with mitoxantrone plus a glucocorticoid has been reported to provide palliation but no survival benefit, as compared with a glucocorticoid alone.[11,12]

Sipuleucel-T is an active cellular immunotherapy, a type of therapeutic cancer vaccine,[13] consisting of autologous peripheral-blood mononuclear cells (PBMCs), including antigen-presenting cells (APCs), that have been activated ex vivo with a recombinant fusion protein (PA2024). PA2024 consists of a prostate antigen, prostatic acid phosphatase, that is fused to granulocyte–macrophage colony-stimulating factor, an immune-cell activator.

In a randomized, placebo-controlled trial involving 127 patients with metastatic castration-resistant prostate cancer, men in the sipuleucel-T group had a relative reduction in the risk of death of 41%, as compared with those in the placebo group (hazard ratio in the sipuleucel-T group, 0.59; 95% confidence interval [CI], 0.39 to 0.88; P=0.01).[14,15] A second randomized, placebo-controlled study showed a trend toward increased survival with sipuleucel-T, although it was not statistically significant.[15] These studies did not show a significant effect on the time to disease progression, the primary end point of both trials. To confirm these survival findings, we conducted a double-blind, placebo-controlled, multicenter trial, called the Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) study, involving 512 men with metastatic castration-resistant prostate cancer, with overall survival as the primary end point.

METHODS

PATIENTS

Eligible men had metastatic castration-resistant prostate cancer and an expected survival of at least 6 months. A previous randomized trial of sipuleucel-T[14] suggested a positive effect on disease progression in men with increased tumor differentiation at diagnosis, as indicated by a Gleason score of 7 or less (on a scale of 2 to 10, with higher scores indicating more aggressive disease). On the basis of these results, we initially enrolled only men with a Gleason score of 7 or less. In addition, only patients with asymptomatic disease were enrolled. After the overall survival analysis in the aforementioned trial, which indicated a positive treatment effect that was independent of the Gleason score, we amended the eligibility criteria to include men with any Gleason score, as well as those whose disease was minimally symptomatic.

Additional eligibility criteria were a serum prostate-specific antigen (PSA) level of 5 ng per milliliter or more and a serum testosterone level of less than 50 ng per deciliter (17 nmol per liter). Exclusion criteria were an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or more (on a scale from 0 to 5, with higher scores indicating greater disability),[16] visceral metastases, pathologic long-bone fractures, spinal cord compression, and treatment within the previous 28 days with systemic glucocorticoids, external-beam radiation, surgery, or systemic therapy for prostate cancer (except medical or surgical castration). Patients were also excluded if they had initiated or discontinued bisphosphonate therapy within the previous 28 days, if they had undergone previous treatment with more than two chemotherapy regimens, or if they had undergone chemotherapy within the previous 3 months. Continuation of medical castration or bisphosphonate therapy was required at least until the time of disease progression.

The study was conducted in accordance with applicable regulations of the Food and Drug Administration and the Good Clinical Practice guidelines of the International Conference on Harmonization. The study was approved by the institutional review board at each study center. Patients provided written informed consent before participation.

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RANDOMIZATION AND TREATMENT

Patients were randomly assigned in a 2:1 ratio to receive either sipuleucel-T or placebo every 2 weeks, for a total of three infusions. All patients were stratified according to the primary Gleason grade (≤3 or ≥4, on a scale of 1 to 5, with higher grades indicating a worse prognosis), the number of bone metastases (≤5, 6 to 10, or >10), and bisphosphonate use (yes or no) with the use of Pocock and Simon's minimization method.[17]

Patients were scheduled for three leukapheresis procedures (at weeks 0, 2, and 4), each followed approximately 3 days later by infusion of sipuleucel-T or placebo. Infusions were prepared from PBMCs collected by means of a single standard leukapheresis processing 1.5 to 2.0 times the patient's estimated blood volume.

Sipuleucel-T was prepared at a central manufacturing facility by culturing APCs for 36 to 44 hours at 37°C with media containing PA2024.[14,18-20] The cells were washed before final formulation. Placebo was prepared by culturing APCs from one third of the leukapheresis collection in medium for 36 to 44 hours at 2 to 8°C, without PA2024. Remaining cells were cryopreserved for possible use in a salvage study, as described in the following paragraph. Each dose of sipuleucel-T or placebo contained a minimum of 40 million large cells expressing the costimulatory molecule CD54. After premedication with acetaminophen and an antihistamine, patients received sipuleucel-T or placebo intravenously during a period of approximately 60 minutes and were then observed for at least 30 minutes.

Objective disease progression was monitored by means of computed tomography (CT) (at weeks 6, 14, 26, and 34 and every 12 weeks thereafter) and bone scanning (at weeks 6, 10, 14, 18, 22, 26, and 34 and every 12 weeks thereafter). Serum for blood chemical analysis, including PSA, was obtained according to the CT schedule until disease progression. A subgroup of patients was monitored for measures of immune function at weeks 6, 14, and 26. After central confirmation of disease progression, the treatment assignment could be revealed to patients, who were then treated at the physician's discretion. Patients in the placebo group could enroll in an open-label salvage protocol and receive APC8015F, a product manufactured according to the same specifications as sipuleucel-T but from cells cryopreserved at the time the placebo was prepared.

ADVERSE EVENTS

All adverse events were reported until the time of objective disease progression. Thereafter, only events that were determined by investigators to be at least possibly related to sipuleucel-T were reported, except cerebrovascular events, which were reported regardless of causality assessment. Monitoring for treatment-related adverse events and survival occurred 2 and 6 months after disease progression and at intervals of 6 months or less thereafter. The safety population included all patients who had undergone at least one leukapheresis procedure. Adverse events and laboratory values were graded with the use of the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0. Multiple occurrences of specific events were counted once per patient; the event with the greatest severity was summarized. Additional anticancer interventions and causes of death were collected for all patients.

The cutoff date for data presented here was January 18, 2009; at that time the study had reached the number of deaths specified for the primary analysis. The study concluded on April 30, 2009.

STUDY OVERSIGHT

The study was designed, conducted, and analyzed by representatives of the sponsor, Dendreon, in collaboration with study investigators. All the authors were responsible for writing the manuscript and for the decision to submit it for publication. They vouch for the completeness and integrity of the reported data and analyses, as well as the fidelity of the study to the protocol. The protocol is available with the full text of this article at NEJM.org.

STATISTICAL ANALYSIS

Overall survival was the primary study end point. The time to objective disease progression and the time to disease-related pain were the original coprimary end points, but after a review of survival results from two previous phase 3 trials with a similar design[14,15] and before the unblinding of group assignments in our study, we made overall survival the primary end point; the time to objective disease progression became a secondary end point, and the time to disease-related pain was eliminated.

Overall survival was defined as the time from randomization until death from any cause. We

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estimated that we would need to enroll 500 patients in order to analyze 304 deaths, providing a power of at least 88% to detect a relative reduction in the risk of death of 31% in the sipuleucel-T group, as compared with the placebo group (hazard ratio, 0.69) with the use of a two-sided alpha level of 0.05.

One planned interim analysis was conducted by an independent data and safety monitoring committee. On the basis of Lan–DeMets implementation[21,22] of the O'Brien–Fleming alpha spending function, the significance level for the final analysis was adjusted to 0.043, resulting in an overall level of 0.05.

The primary end point of overall survival was analyzed with the use of a two-sided Wald's test for treatment effect on the basis of a stratified Cox regression model with adjustment for the natural log of the baseline levels of PSA and lactate dehydrogenase, stratified according to randomization factors. Measures of PSA and lactate dehydrogenase were included in the model on the basis of their importance as prognostic factors in previous trials of sipuleucel-T[14,15] and other prostate-cancer studies.[23,24] Estimated hazard ratios and corresponding two-sided 95% confidence intervals were generated. Planned sensitivity analyses included an assessment of overall survival with a stratified, unadjusted Cox model and log-rank test; analyses of baseline covariates as effect modifiers; and an assessment of the effect of docetaxel on survival, with first docetaxel use added as a time-dependent covariate in the primary Cox model.[25] Exploratory analyses included a determination of prostate-cancer–specific survival, assessed with the use of the primary Cox model, with deaths from other causes treated as competing events. Median follow-up time was estimated with the use of an inverted Kaplan–Meier technique.

A blinded, independent radiology-review committee determined the time to objective disease progression on the basis of radiographic studies, with one or more of the following criteria used to define progression: an increase of at least 50% in the sum of the products of diameters for index lesions, the new appearance or unequivocal progression of nonindex lesions, at least two new lesions on bone scanning, and a new pathologic fracture or spinal cord compression. The treatment effect was assessed by means of a stratified log-rank test; hazard ratios were estimated with a stratified, unadjusted Cox regression model.

Antibody titers were assessed by means of an enzyme-linked immunosorbent assay,[26] with threshold levels for response defined as 2 SD above the median of the baseline values for all assessed patients. T-cell proliferation was assessed with the use of a stimulation index, calculated as the median value for ^{3}H-thymidine incorporation from triplicate wells cultured with antigen, divided by the median incorporation value in the absence of antigen.[14]

RESULTS

PATIENTS

From August 2003 through November 2007, a total of 512 patients were enrolled at 75 centers in the United States and Canada, with 341 assigned to receive sipuleucel-T and 171 assigned to receive placebo (Fig. 1). Of these patients, 98.8% underwent at least one leukapheresis procedure, 97.1% received at least one infusion of a study drug, and 92.2% received all three infusions. The median time from the first infusion to the third infusion was 28 days (range, 21 to 119).

Demographic and clinical characteristics were similar in the two study groups (Table 1). The median age of the patients was 71 years. All patients had received previous androgen-deprivation therapy; 82.0% reported having undergone combined androgen blockade. Previous therapies also included radiotherapy of the prostate or prostate bed (53.9% of patients), radical prostatectomy (35.2%), and chemotherapy (18.2%).

EFFICACY

By the data-cutoff date on January 18, 2009, a total of 331 patients had died: 210 of the 341 patients in the sipuleucel-T group (61.6%) and 121 of the 171 patients in the placebo group (70.8%). The median follow-up time was 34.1 months. For men in the sipuleucel-T group, as compared with those in the placebo group, the adjusted hazard ratio for death was 0.78 (95% CI, 0.61 to 0.98), representing a relative reduction in the risk of death of 22% (P=0.03). Similar results were obtained with the use of the unadjusted, stratified model and the log-rank test (hazard ratio, 0.77; 95% CI, 0.61 to 0.97; P=0.02). The reduction in the risk of death from prostate cancer in the sipuleucel-T group

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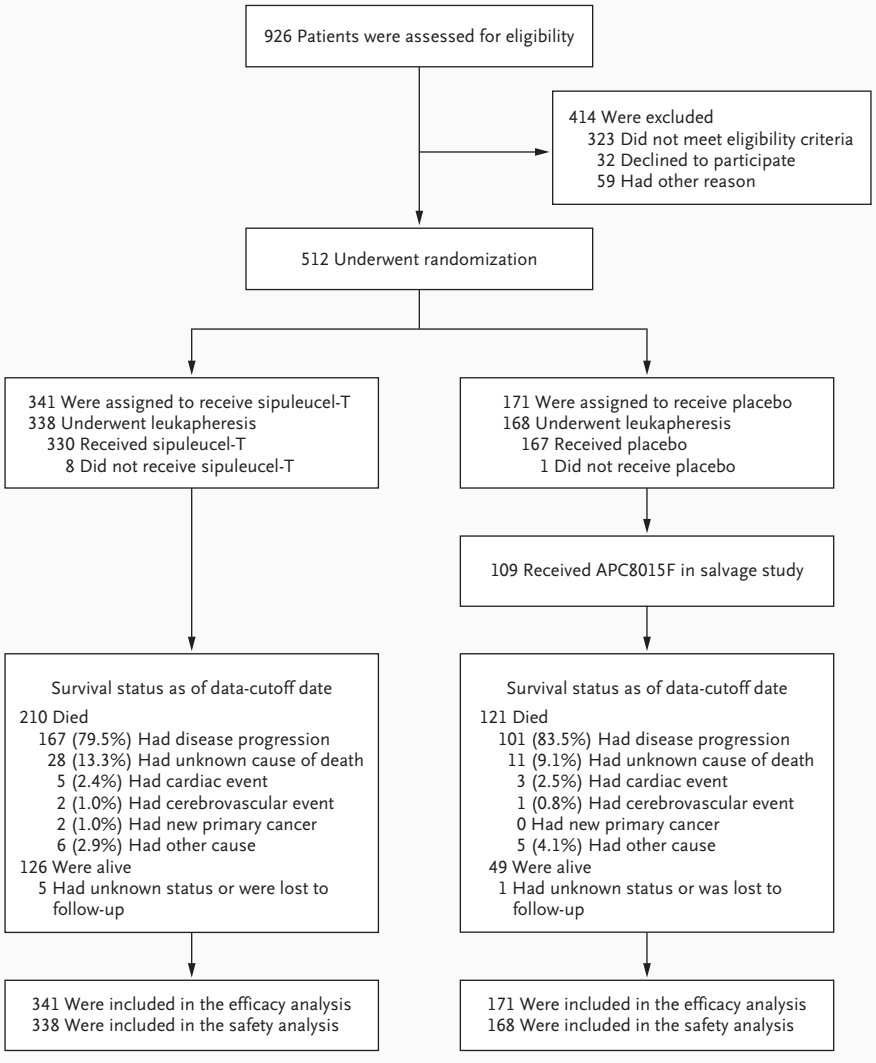


Figure 1. Enrollment and Outcomes.

(hazard ratio, 0.77; 95% CI, 0.61 to 0.98; P=0.04) was similar to the reduction in the risk of death from any cause.

The median survival was 4.1 months longer in the sipuleucel-T group (25.8 months) than in the placebo group (21.7 months) (Fig. 2A). The estimated probability of survival 36 months after randomization was 31.7% in the sipuleucel-T group and 23.0% in the placebo group.

The treatment effect consistently favored the sipuleucel-T group in the assessment of more than 20 baseline characteristics of the patients as effect modifiers (Fig. 3). Therapy with sipuleucel-T was also associated with a positive overall survival effect in an analysis that included 18 additional deaths observed between the data-cutoff and study-completion dates, with a median of 36.5 months of follow-up (hazard ratio, 0.76; 95% CI, 0.61 to 0.95; P=0.02).

The median time to objective disease progression was 14.6 weeks (3.7 months) in the sipuleucel-T group and 14.4 weeks (3.6 months) in the placebo group (hazard ratio, 0.95; 95% CI, 0.77 to 1.17; P=0.63). Similar results were observed for the time to clinical disease progression (hazard ratio, 0.92; 95% CI, 0.75 to 1.12; P=0.40). One pa-

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tient in the sipuleucel-T group had a partial objective response. Among patients with PSA assessments after baseline, reductions of at least 50% on two visits at least 4 weeks apart were observed in 8 of 311 patients (2.6%) in the sipuleucel-T group, as compared with 2 of 153 patients (1.3%) in the placebo group.

IMMUNE RESPONSE

Titers of antibodies against the immunizing antigen PA2024 that exceeded 400 at any time after baseline were observed in 100 of 151 patients (66.2%) in the sipuleucel-T group and 2 of 70 patients (2.9%) in the placebo group; titers of antibodies against prostatic acid phosphatase that exceeded 400 at any time after baseline were observed in 43 of 151 patients (28.5%) in the sipuleucel-T group and 1 of 70 patients (1.4%) in the placebo group.

At week 6, T-cell proliferation responses (stimulation index, >5) to PA2024 were observed in 46 of 63 patients (73.0%) in the sipuleucel-T group

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Characteristic	Sipuleucel-T (N=341)	Placebo (N=171)
Median age (range) — yr	72 (49–91)	70 (40–89)
Race — %†		
White	89.4	91.2
Black	6.7	4.1
Other	3.8	4.7
Median time since diagnosis (range) — yr	7.1 (0.8–24.5)	7.1 (0.9–21.5)
Median predicted survival — mo‡	20.3	21.2
ECOG performance status of 0 — %§	82.1	81.3
Gleason score ≤7 — %¶	75.4	75.4
Primary Gleason grade — %¶‖		
≤3	42.2	41.5
≥4	57.8	58.5
Disease location — % **		
Bone only	50.7	43.3
Soft tissue only	7.0	8.2
Bone and soft tissue	41.9	48.5
No. of bone metastases — %‖		
0–5	42.8	42.7
6–10	14.4	14.6
>10	42.8	42.7
Bisphosphonate use — %‖	48.1	48.0
Previous prostate-cancer therapy — %		
Androgen-deprivation therapy	100.0	100.0
Combined androgen blockade	81.8	82.5
Medical or surgical castration alone	18.2	17.5
Orchiectomy	9.4	7.6
Chemotherapy	19.6	15.2
Docetaxel	15.5	12.3
Radical prostatectomy	35.5	34.5
Radiation to prostate or prostate bed	54.3	53.2
Baseline pain score — %††		
0	51.5	52.6
≥0	48.5	47.4

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Table 1. (Continued.)

Characteristic	Sipuleucel-T (N=341)	Placebo (N=171)
Median laboratory values		
Serum prostate-specific antigen — ng/ml‡‡	51.7	47.2
Serum prostatic acid phosphatase — U/liter§§	2.7	3.2
Alkaline phosphatase — U/liter¶¶	99	109
Hemoglobin — g/dl	12.9	12.7
Lactate dehydrogenase — U/liter	194	193
White-cell count — cells/mm^3	6200	6000
Total absolute neutrophil count — cells/mm^3	4000	4100

* Percentages may not total 100 because of rounding.
† Race was self-reported.
‡ The prognostic model that was used to calculate this value is from Halabi et al.[23]
§ Patients with an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1 were included in the study, with 0 indicating that the patient is fully active and able to carry on all predisease activities without restriction, and 1 indicating that the patient is restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature.[16]
¶ The Gleason grade ranges from 1 to 5, with higher numbers indicating less differentiated tumors. The Gleason score is the sum of the grades for the most common and second most common tumor patterns, with a score of more than 7 indicating high-grade and more aggressive disease.
‖ This category was used as a stratification factor at baseline.
** Data regarding disease location were missing for one patient in the sipuleucel-T group.
†† Data regarding pain were missing for three patients in the sipuleucel-T group.
‡‡ Normal values for prostate-specific antigen range from 2.7 ng per milliliter or less for men between the ages of 40 and 50 years to 7.2 ng per milliliter or less for men 80 years of age or older.
§§ The normal range for serum prostatic acid phosphatase for men of all ages is 0.1 to 1.2 U per liter.
¶¶ The normal range for alkaline phosphatase is 31 to 131 U per liter, depending on age.

and 4 of 33 patients (12.1%) in the placebo group; such responses to prostatic acid phosphatase were observed in 15 of 55 patients (27.3%) in the sipuleucel-T group and 2 of 25 patients (8.0%) in the placebo group.

In prespecified analyses, patients in the sipuleucel-T group who had an antibody titer of more than 400 against PA2024 or prostatic acid phosphatase at any time after baseline lived longer than did those who had an antibody titer of 400 or less ($P<0.001$ and $P=0.08$, respectively, by the log-rank test). No survival difference could be detected between patients in the sipuleucel-T group who had T-cell proliferation responses to PA2024 or prostatic acid phosphatase at week 6 and those who did not.

THERAPIES RECEIVED AFTER STUDY TREATMENT

Of the 171 patients in the placebo group, 84 (49.1%) received APC8015F as the first additional anticancer intervention after the completion of the study treatment, and a total of 109 patients (63.7%) received APC8015F at some point. The estimated median survival in the placebo group was 23.8 months for patients who were subsequently treated with APC8015F and 11.6 months for those who did not receive APC8015F. Since this comparison was not randomized, the effect of frozen product APC8015F would need to be evaluated prospectively.

Overall, additional anticancer treatments (other than APC8015F) were administered in 279 of the 341 patients (81.8%) in the sipuleucel-T group and 125 of the 171 patients (73.1%) in the placebo group. These therapies included docetaxel, received by 195 patients (57.2%) in the sipuleucel-T group and 86 patients (50.3%) in the placebo group. The Kaplan–Meier estimate of the median time to docetaxel use was 12.3 months in the sipuleucel-T group and 13.9 months in the placebo group. The effect of docetaxel in the sipuleucel-T group was assessed by means of the primary Cox model, with adjustment for the use of docetaxel and for the timing of its initiation. In this analysis, the estimated effect of sipuleucel-T treatment (hazard ratio for death, 0.78; 95% CI, 0.62 to 0.98; $P=0.03$) was consistent with the result of the primary efficacy analysis, and there was also a trend toward a beneficial effect of docetaxel use that was independent of the study-group assignment

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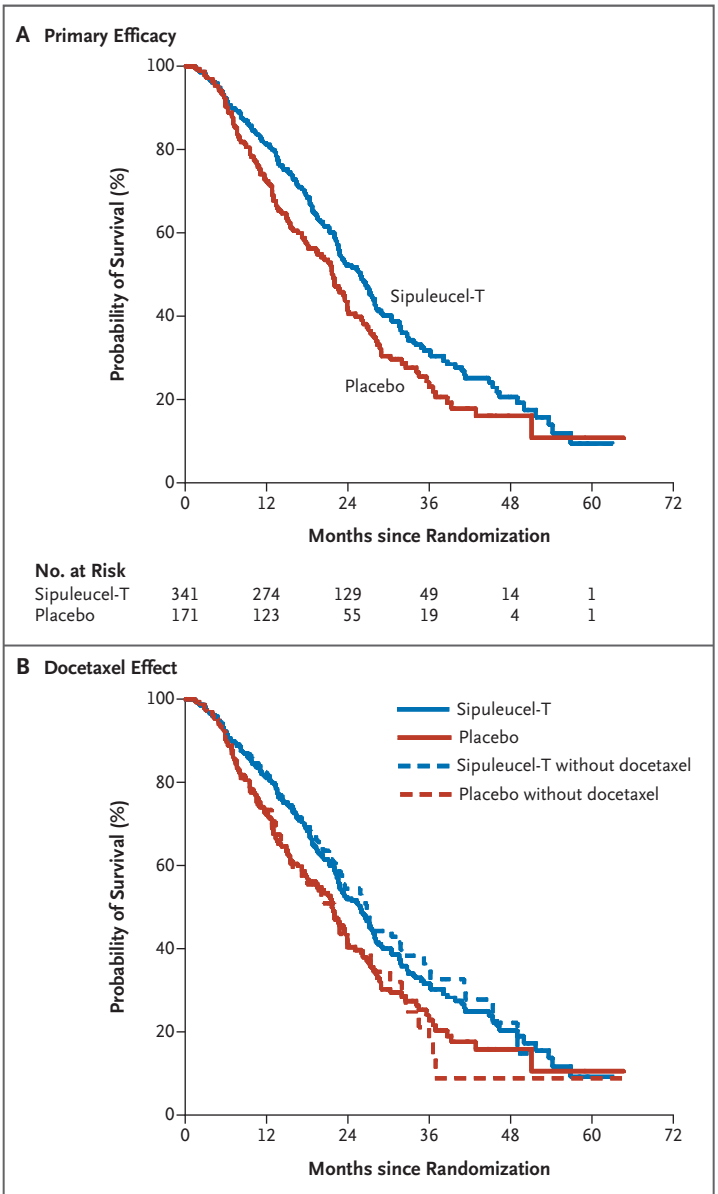


Figure 2. Kaplan–Meier Estimates of Overall Survival.

Panel A shows 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 to 0.98; P=0.03). Panel B shows the results of the analysis with and without censoring at the time of the initiation of docetaxel therapy after study treatment. After censoring at the time of docetaxel initiation, a consistent treatment effect with sipuleucel-T was observed (hazard ratio, 0.65; 95% CI, 0.47 to 0.90; P=0.009). Statistical approaches to assess the effects of subsequent treatment vary; no consensus exists on how to address the confounding effects.

(hazard ratio, 0.88; P=0.30). Furthermore, within each study group, survival curves were similar with and without censoring[27] at the initiation of docetaxel use (Fig. 2B). These results suggest that the sipuleucel-T treatment effect was not explained by differences in the frequency or timing of subsequent docetaxel use in the two study groups.

SAFETY

Adverse events were reported for 496 of 506 patients (98.0%) in the safety population and were mild to moderate (grade 1 or 2) for 330 patients (65.2%). Adverse events that were reported more frequently in the sipuleucel-T group than in the placebo group included chills, fever (pyrexia), headache, influenza-like illness, myalgia, hypertension, hyperhidrosis, and groin pain (Table 2). Except for groin pain, most of these events occurred within 1 day after infusion and resolved within 1 to 2 days. Adverse events that were reported more frequently in the placebo group included anorexia, anxiety, depression, flank pain, and contusion, as well as hydronephrosis (in 7.1% of patients in the placebo group vs. 3.8% in the sipuleucel-T group).

The most common adverse events in the sipuleucel-T group within 1 day after infusion were chills (in 51.2%), fever (22.5%), fatigue (16.0%), nausea (14.2%), and headache (10.7%). Adverse events of grade 3 or more within 1 day after infusion were reported in 23 of 338 patients (6.8%) in the sipuleucel-T group and 3 of 168 patients (1.8%) in the placebo group. Among patients in the sipuleucel-T group, grade 3 events that were reported for at least 1 patient within 1 day after infusion were chills (in 4 patients), fatigue (3 patients), and back pain, hypertension, hypokalemia, and muscular weakness (in 2 patients each); one grade 4 event was reported (intravenous catheter–associated bacteremia). Overall, only 3 of 338 patients (0.9%) in the sipuleucel-T group were unable to receive all three infusions because of infusion-related adverse events.

Cerebrovascular events were reported for 8 of 338 patients (2.4%) in the sipuleucel-T group and 3 of 168 patients (1.8%) in the placebo group (P=1.00 by Fisher's exact test). The incidence rate was 1.33 cerebrovascular events per 100 person-years (95% CI, 0.58 to 2.62) in the sipuleucel-T group and 1.11 per 100 person-years (95% CI, 0.23 to 3.24) in the placebo group. The median interval between the most recent infusion and the event was 210 days in the sipuleucel-T group and 196 days in the placebo group.

DISCUSSION

In our study, treatment with the therapeutic cancer vaccine sipuleucel-T led to a significant im-

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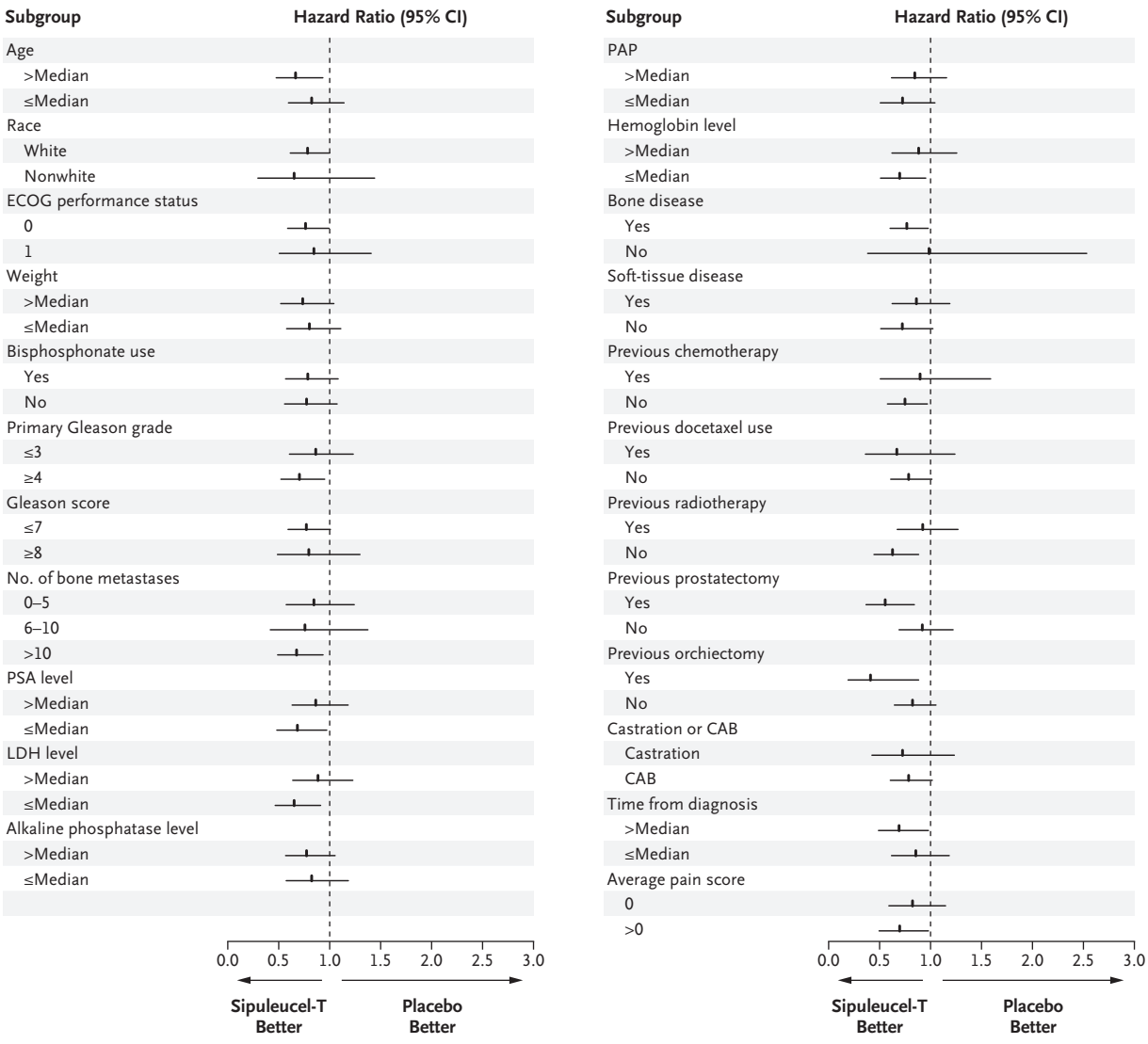


Figure 3. Hazard Ratios for the Risk of Death, According to Subgroup.

The forest plot shows hazard ratios according to baseline characteristics of the patients in the sipuleucel-T group and the placebo group. Subgroup analyses were prespecified for 19 variables (including 1 variable, bone or soft-tissue disease, that was split into two analyses and 1 variable, age, for which the median cut-point was not prespecified), and there were three post hoc analyses (castration or combined androgen blockade [CAB], previous orchiectomy, and average pain score). Missing values for baseline characteristics were not imputed. ECOG denotes Eastern Cooperative Oncology Group, LDH lactate dehydrogenase, PAP prostatic acid phosphatase, and PSA prostate-specific antigen.

provement in overall survival for men with metastatic castration-resistant prostate cancer. With a median follow-up of 34.1 months and complete survival follow-up data for 99% of patients, treatment with sipuleucel-T resulted in a 4.1-month improvement in median survival and an improvement in the rate of 3-year survival (31.7% for patients receiving sipuleucel-T, as compared with 23.0% for those receiving placebo). These results are consistent with and confirm the findings of a randomized trial,[14] in which the sipuleucel-T group had a 3-year survival rate of 34.1%, a median increase in survival of 4.5 months, and a median survival of 25.9 months (25.8 months in our study). However, our results differ from those of a smaller trial,[15] in which no significant survival advantage was observed with sipuleucel-T.

In our study, the effect of sipuleucel-T on survival was observed consistently across subgroups of patients, including those with prognostic fac-

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Table 2. Adverse Events.*

Event	Sipuleucel-T (N=338)		Placebo (N=168)	
	All Grades	Grade 3–5	All Grades	Grade 3–5
	number (percent)			
Any	334 (98.8)	107 (31.7)	162 (96.4)	59 (35.1)
Chills†	183 (54.1)	4 (1.2)	21 (12.5)	0
Fatigue	132 (39.1)	4 (1.2)	64 (38.1)	3 (1.8)
Back pain	116 (34.3)	12 (3.6)	61 (36.3)	8 (4.8)
Pyrexia†	99 (29.3)	1 (0.3)	23 (13.7)	3 (1.8)
Nausea	95 (28.1)	2 (0.6)	35 (20.8)	0
Arthralgia	70 (20.7)	7 (2.1)	40 (23.8)	5 (3.0)
Citrate toxicity‡	68 (20.1)	0	34 (20.2)	0
Vomiting	60 (17.8)	0	20 (11.9)	0
Headache†	54 (16.0)	1 (0.3)	8 (4.8)	0
Anemia	50 (14.8)	5 (1.5)	21 (12.5)	7 (4.2)
Limb pain	49 (14.5)	4 (1.2)	25 (14.9)	1 (0.6)
Dizziness	49 (14.5)	0	16 (9.5)	0
Paresthesia‡	45 (13.3)	0	26 (15.5)	0
Constipation	45 (13.3)	0	24 (14.3)	2 (1.2)
Musculoskeletal pain	44 (13.0)	3 (0.9)	20 (11.9)	3 (1.8)
Pain§	44 (13.0)	6 (1.8)	12 (7.1)	2 (1.2)
Paresthesia (oral)‡	41 (12.1)	0	21 (12.5)	0
Asthenia	37 (10.9)	6 (1.8)	13 (7.7)	2 (1.2)
Diarrhea	36 (10.7)	1 (0.3)	17 (10.1)	3 (1.8)
Musculoskeletal chest pain	33 (9.8)	2 (0.6)	19 (11.3)	2 (1.2)
Myalgia†	33 (9.8)	2 (0.6)	8 (4.8)	0
Influenza-like illness†	33 (9.8)	0	6 (3.6)	0
Bone pain	32 (9.5)	3 (0.9)	18 (10.7)	2 (1.2)
Hypertension†	25 (7.4)	2 (0.6)	5 (3.0)	0
Anorexia	24 (7.1)	1 (0.3)	27 (16.1)	3 (1.8)
Weight loss	20 (5.9)	2 (0.6)	18 (10.7)	1 (0.6)
Hyperhidrosis†	18 (5.3)	0	1 (0.6)	0
Groin pain†	17 (5.0)	0	4 (2.4)	0
Anxiety	13 (3.8)	0	14 (8.3)	0
Flank pain	9 (2.7)	0	10 (6.0)	0
Contusion	9 (2.7)	0	9 (5.4)	0
Depression	8 (2.4)	1 (0.3)	11 (6.5)	0

* Listed are all adverse events that were reported by at least 10% of patients in either study group or by at least 5% of patients in either study group if the incidence varied by a factor of 2 or more between the two groups. Adverse events were coded with the use of the preferred terms listed in the *Medical Dictionary for Regulatory Activities, 11th Edition*.

† The incidence of adverse events in this category was higher by a factor of 2 or more in the sipuleucel-T group than in the placebo group.

‡ Citrate toxicity has been associated with leukapheresis; paresthesia and oral paresthesia are likely symptoms of citrate toxicity.

§ The preferred terms reflect adverse events as reported by investigators, so it is not possible to distinguish the various classifications of pain.

tors known to be adversely correlated with overall survival, such as increased levels of PSA, lactate dehydrogenase, and alkaline phosphatase, as well as an increased number of bone metastases, an increased Gleason score, a decreased performance status, and the presence of pain.[14,23,24]

The majority of patients in both study groups received docetaxel after study treatment. Statistical methods that are used to address postbaseline confounding factors in any randomized clinical study are limited and subject to potential biases. Specifically, the selection of patients who received docetaxel may have confounded the estimation of the docetaxel effect. Nevertheless, sensitivity analyses did not provide evidence that between-group differences in the use of docetaxel could account for the observed treatment difference with respect to overall survival.

The crossover study design was unusual for a trial with a survival end point and was a legacy of the original primary study end point, the time to objective disease progression. Nonetheless, the survival effect with sipuleucel-T was observed despite the inclusion of optional APC8015F salvage therapy for placebo-treated patients. The 21.7-month median survival of patients in the placebo group compares favorably with that in control groups in other randomized trials involving similar patient populations (range, 15.5 to 21.7 months),[3,5,6,10,28-31] indicating that the treatment effect cannot be attributed to a poor outcome in the placebo group.

In contrast to overall survival, the time to objective disease progression as defined in this study did not differ significantly between the study groups. This result is consistent with the findings in previous trials of sipuleucel-T and may be due to the delayed onset of antitumor responses after active immunotherapy, relative to objective disease progression, which occurred early in this group of patients.[32] In patients with metastatic castration-resistant prostate cancer, the disease-progression end point, as currently defined, has not been a reliable predictor of overall survival. Several randomized trials that have shown effects of various treatments on overall survival have not shown effects on disease progression[14,28,29] and vice versa,[7] including one study in which a therapeutic prostate cancer vaccine was administered in a patient population similar to ours,[29] suggesting a possible class effect or some previously unknown feature of prostate cancer.

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In general, sipuleucel-T was well tolerated, and most patients received all three scheduled infusions. Adverse events that were more frequently reported for sipuleucel-T treatment than for placebo were generally consistent with the release of cytokines.[33] We did not observe an increased incidence of cerebrovascular events after sipuleucel-T treatment, as reported in previous randomized trials.[15] There were no reports of anaphylaxis after sipuleucel-T administration, and there was no evidence of autoimmune sequelae.

In conclusion, sipuleucel-T prolonged survival among men with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer. However, no significant effect on the time to objective disease progression was observed. The treatment was associated with infusional adverse events, including fever and chills, which were mainly grade 1 or 2 in severity. Treatment was completed in approximately 1 month and did not preclude subsequent therapies, including chemotherapy.

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APPENDIX

In addition to the authors, the following principal clinical investigators participated in this trial: T. Ahmed, A. Amin, J. Arseneau, N. Barth, G. Bernstein, B. Bracken, P. Burch, V. Caggiano, J. Chin, G. Chodak, F. Chu, J. Corman, B. Curti, N. Dawson, J.F. Deeken, T. Dubernet, M. Fishman, R. Flanigan, F. Gailani, L. Garbo, T. Gardner, E. Gelmann, D. George, T. Godfrey, L. Gomella, M. Guerra, S. Hall, J. Hanson, R. Israeli, E. Jancis, M.A.S. Jewett, V. Kassabian, J. Katz, L. Klotz, H. Koh, R. Kratzke, R. Lance, J. Lech, L. Leichman, R. Lemon, J. Liang, J. Libertino, M. Lilly, I. Malik, S.E. Martin, J. McCaffrey, D. McLeod, D. McNeel, B. Miles, M. Murdock, C. Nabhan, J. Nemunaitis, D. Notter, A. Pantuck, P. Perrotte, D. Pessis, D. Petrylak, J. Polikoff, P. Pommerville, S. Ramanathan, M. Rarick, J. Richards, R. Rifkin, N. Rohatgi, R. Rosenbluth, R. Santucci, A. Sayegh, J. Seigne, I. Shapira, N. Shedhadeh, D. Shepherd, S. Sridhar, R. Stephenson, C. Teigland, N. Thaker, J. Vacirca, L. Villa, Jr., N. Vogelzang, M. Wertheim, J.H. Wolff, R. Wurzel, C. Yang, J. Young.

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