

CELLULAR, TISSUE AND GENE THERAPIES ADVISORY COMMITTEE

SIPULEUCEL-T BRIEFING DOCUMENT

BLA STN 125197/0

“Sipuleucel-T is an autologous active cellular immunotherapy indicated for the treatment of men with asymptomatic metastatic androgen independent prostate cancer.”

For CTGTAC Meeting: March 29, 2007

Dendreon Corporation

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

1.0 EXECUTIVE OVERVIEW

Management of patients with advanced androgen independent prostate cancer (AIPC) remains a significant clinical challenge, as most of these men die from their disease, and current treatment options are limited. Numerous trials conducted in men with metastatic AIPC have led to a limited number of approved therapies; only 1 of these drugs, docetaxel, has been shown to confer a survival advantage. There is a clear need for additional therapeutic options for patients with advanced AIPC, particularly since many of these patients elect not to pursue chemotherapy ([Kirk, 2006](#)).

If approved, sipuleucel-T will be the first of a new class of therapies designed to stimulate a patient's own immune system against cancer. Sipuleucel-T consists of a patient's autologous peripheral blood mononuclear cells (PBMCs), including antigen presenting cells (APCs), that have been activated in vitro with a recombinant fusion protein. The recombinant fusion protein (PA2024) is a prostate antigen fused to granulocyte-macrophage colony-stimulating factor (GM-CSF), an immune cell activator. While its precise mechanism of action is unknown, sipuleucel-T potency (a measure of activated APCs) correlates with overall survival.

Double blind, randomized controlled trials have demonstrated that sipuleucel-T prolongs survival in men with asymptomatic metastatic AIPC and treatment is very well tolerated.

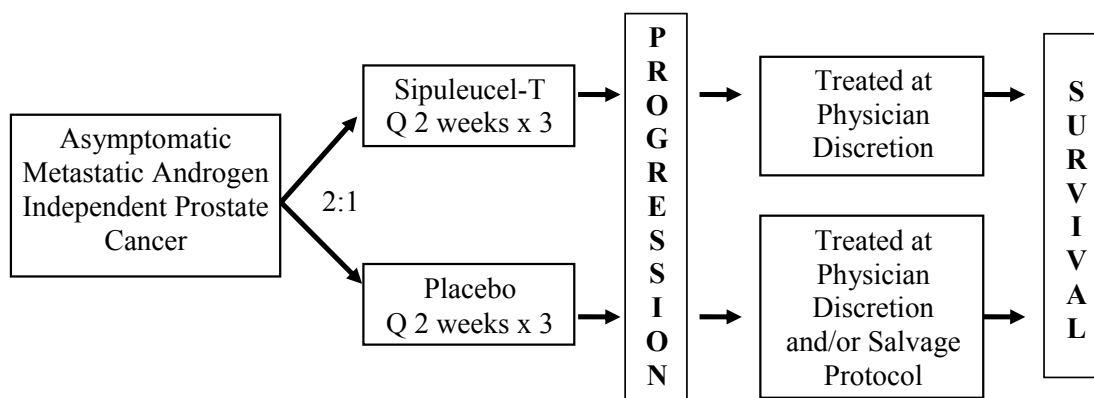
1.1 Background Information on Phase III Program

There are 2 Phase III studies of sipuleucel-T in this submission. The studies were parallel, multicenter, randomized, double blind, placebo-controlled trials comparing intravenous (IV) infusion of sipuleucel-T to a control infusion (autologous PBMCs without antigen and activation) in AIPC patients. The studies were designated D9901 (Study 1) and D9902A (Study 2) and will be referred to as Study 1 and Study 2 throughout this briefing document. The original intent of Studies 1 and 2 was to evaluate the ability of sipuleucel-T to delay the time to disease progression (TTP), the primary endpoint, in patients with asymptomatic metastatic AIPC. Additionally, while the studies were not prospectively powered to detect a treatment difference in overall survival, the protocol and statistical analysis plan specified that all patients were to be followed for overall survival until 36 months post-randomization.

In Studies 1 and 2, patients were randomized 2:1 (sipuleucel-T:placebo). Sipuleucel-T was infused intravenously at Weeks 0, 2, and 4, and patients were then followed for the study endpoints. The primary endpoint of Study 1 was TTP (Figure 1), defined by any of the following:

- Progressive disease on serial radiographic imaging tests (tumor staging was performed at baseline, Weeks 8, 16, 24, and 32, and every 12 weeks thereafter until disease progression),
- New cancer-related pain associated with a radiographic anatomical correlation, or
- Other clinical events consistent with progression such as spinal cord compression, nerve root compression, or pathologic fracture.

Figure 1 Treatment Schema



At the time that patients were confirmed to have developed disease progression, study treatment could be unblinded, and patients were then treated at the physician's discretion. Patients in the placebo group had the option to enter a Phase II, open label, single-arm salvage trial (Protocol D9903) in which they received a version of sipuleucel-T prepared from the cryopreserved cells remaining after placebo generation.

In 2002, Dendreon analyzed the Study 1 results for the primary endpoint in Study 1, TTP. A trend toward delayed TTP was observed that did not reach statistical significance in the randomized (intent-to-treat [ITT]) population. Based on the results of Study 1, it was unlikely that Study 2 would meet the primary endpoint of TTP. Therefore, enrollment in Study 2 was

stopped early, but the study remained blinded. Dendreon then met with Food and Drug Administration (FDA) to discuss the design of a new Phase III study, Study D9902B (Study 3), based on the knowledge gained from the analysis of the primary endpoint of Study 1. All patients in both Studies 1 and 2 continued to be followed for survival.

In 2004, the 36-month follow-up was complete for all Study 1 patients, and the analysis demonstrated a 41% reduced risk of death for patients randomized to treatment with sipuleucel-T compared to patients randomized to treatment with placebo (hazard ratio [HR] = 1.71 [95% confidence interval (CI): 1.13, 2.58]; $P = 0.010$; [Table 1](#)). The overall survival results from Study 2, analyzed in 2005, showed a similar trend. (Note that unless otherwise noted, HRs are calculated with the sipuleucel-T arm used as the denominator, such that a $HR > 1.0$ favors sipuleucel-T.)

These results were discussed with FDA, sipuleucel-T was granted Fast Track designation for asymptomatic metastatic AIPC, and the Biologic License Application (BLA) is under priority review.

1.2 Basis for Licensure

The proposed basis for licensure is the improvement in overall survival seen in the randomized, double blind, placebo-controlled trial, Study 1, supported by the strong trend toward a delay in TTP in this study. Specifically, in Study 1, the survival results are clinically meaningful, statistically persuasive, and internally consistent in the ITT population. Multiple sensitivity analyses all confirm the survival benefit.

Supportive evidence of clinical efficacy in Study 1 is provided by the trend toward prolonged survival in Study 2 and the survival results of the integrated analysis of Studies 1 and 2. A summary of the overall survival results in these studies is presented in [Table 1](#). The clinical findings are further corroborated by the observation that a product specific attribute, potency, correlates with survival. Data from Studies 1 and 2 demonstrate that cumulative CD54 upregulation correlates with overall survival and that the correlation is independent of known prognostic factors in patients with AIPC. Sipuleucel-T is safe and well tolerated, providing an

appealing benefit-to-risk profile to patients and physicians seeking additional options to treat men with asymptomatic metastatic AIPC.

Table 1 Summary of Overall Survival in Studies 1 and 2

	Study 1 N = 127^a	Study 2 N = 98^b	Integrated Study 1 & Study 2 N = 225^c
HR ^d (95% CI)	1.71 (1.13, 2.58)	1.27 (0.78, 2.07)	1.50 ^e (1.10, 2.05)
Log rank p-value	<i>P</i> = 0.010	<i>P</i> = 0.331	<i>P</i> = 0.011 ^e
Median Survival in Months (95% CI)			
Sipuleucel-T	25.9 (20.0, 32.4)	19.0 (13.6, 31.9)	23.2 (19.0, 31.0)
Placebo	21.4 (12.3, 25.8)	15.7 (12.8, 25.4)	18.9 (13.5, 25.3)
Median Survival Benefit in Months	4.5	3.3	4.3
36-Month Survival (%)			
Sipuleucel-T	34%	32%	33%
Placebo	11%	21%	15%

^a Sipuleucel-T arm: n = 82; placebo arm: n = 45

^b Sipuleucel-T arm: n = 65; placebo arm: n = 33

^c Sipuleucel-T arm: n = 147; placebo arm: n = 78

^d An HR greater than 1.0 favors sipuleucel-T.

^e Stratified by protocol (Study 1/Study 2).

Abbreviation: CI = confidence interval; HR = hazard ratio.

1.3 Evidence of Clinical Efficacy

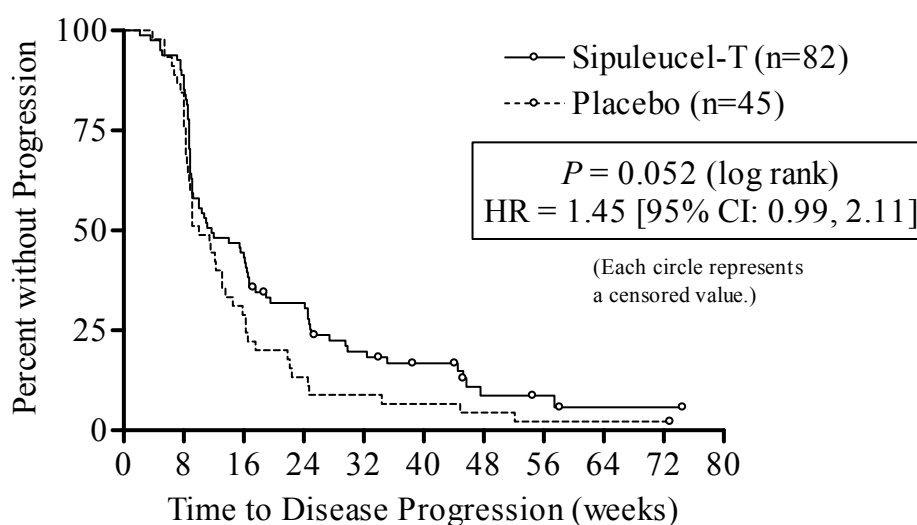
1.3.1 Study 1: Multicenter, Randomized, Double Blind, Placebo-Controlled Trial of Sipuleucel-T in Men with Asymptomatic, Metastatic AIPC

1.3.1.1 Primary Endpoint: Time to Disease Progression

There were 127 patients with asymptomatic metastatic AIPC randomized 2:1 to receive sipuleucel-T (n = 82) or placebo (n = 45) at 19 clinical study centers in the United States. Patients treated with sipuleucel-T demonstrated a 31% reduction in the risk of TTP relative to those treated with placebo (HR = 1.45 [CI: 0.99, 2.11], *P* = 0.052; [Figure 2](#)). The estimated

median TTP was 11.7 weeks in the sipuleucel-T group compared with 10.0 weeks in the placebo group. Consistent with the separation of the Kaplan-Meier curves in Figure 2, this difference was greater at the 75th percentile, where the TTP was 25.0 weeks in the sipuleucel-T group compared with 16.3 weeks in the placebo group. At 24 weeks, 31.9% of the subjects treated with sipuleucel-T and 13.3% of the subjects treated with placebo were progression-free.

Figure 2 Overall Time to Disease Progression in Study 1 (Kaplan-Meier Method), ITT Population



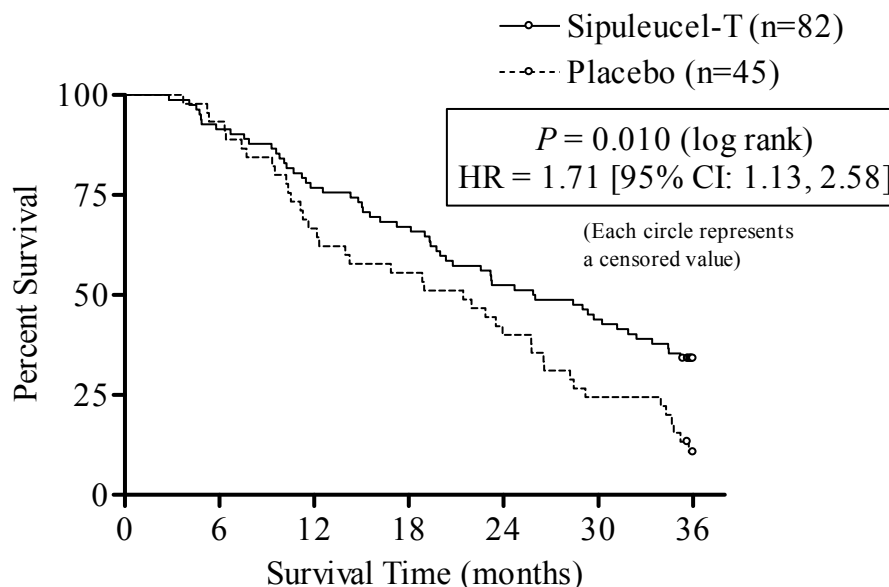
The results of the secondary endpoints of time to clinical progression, time to treatment failure, and time to disease-related pain (TDRP) showed trends in the same direction as TTP with the treatment effect in favor of sipuleucel-T (all p-values > 0.05).

1.3.1.2 Primary Evidence of Clinical Benefit: Overall Survival

Overall survival was calculated using the log rank test; time-to-event percentiles were based on the Kaplan-Meier method. The results demonstrated the following:

- A clinically meaningful and statistically persuasive overall survival benefit; patients treated with sipuleucel-T had a 41% reduced risk of death compared to patients treated with placebo (HR = 1.71 [95% CI: 1.13, 2.58]; $P = 0.010$; [Figure 3](#), in the ITT population). All 127 patients were followed until death or up to 36 months following randomization; there was no early censoring.

Figure 3 Study 1 Overall Survival (Kaplan-Meier Method), ITT Population



- A 4.5 month increase in the median survival of patients treated with sipuleucel-T compared to patients treated with placebo (25.9 months for sipuleucel-T versus 21.4 months for placebo).
- An increase in the percentage of patients alive at the pre-specified cut-off of 36 months following randomization, with 34% (n = 28) of patients treated with sipuleucel-T alive compared to 11% (n = 5) of patients treated with placebo.

The survival result was robust as determined by multiple sensitivity analyses:

- Evidence of a positive treatment effect of sipuleucel-T relative to placebo was consistently observed in sub-populations of patients based on 21 potential or known prognostic factors, many well-described in the literature ([Appendix 4](#)).
- After adjusting for the significant baseline prognostic factors (weight, prostate-specific antigen [PSA], lactate dehydrogenase [LDH], bone lesion count, and localization of disease), the survival results remained strong with an HR of 2.16 ([95% CI: 1.33, 3.50]; $P = 0.002$).

- Evaluation of chemotherapy use and time to chemotherapy revealed no imbalance between the 2 arms, and the treatment effect remained strong after adjustment for the use of docetaxel (HR = 1.54 [95% CI: 1.00, 2.38]; $P = 0.052$).
- Evaluation of prostate cancer specific mortality suggested that the increase in overall survival seen in Study 1 was accompanied by a decrease in prostate cancer specific mortality in the sipuleucel-T arm (HR = 2.04 [95% CI: 1.30, 3.19]; $P = 0.002$).

1.3.2 Supportive Evidence of Clinical Efficacy

Supportive evidence of efficacy is provided from the Study 1 TTP results described above in Section 1.3.1.1. Further supportive evidence includes the overall survival result in Study 2, which showed a trend in favor of sipuleucel-T prolonging survival, the integrated Study 1 and 2 survival results, and a strong correlation between product potency and overall survival.

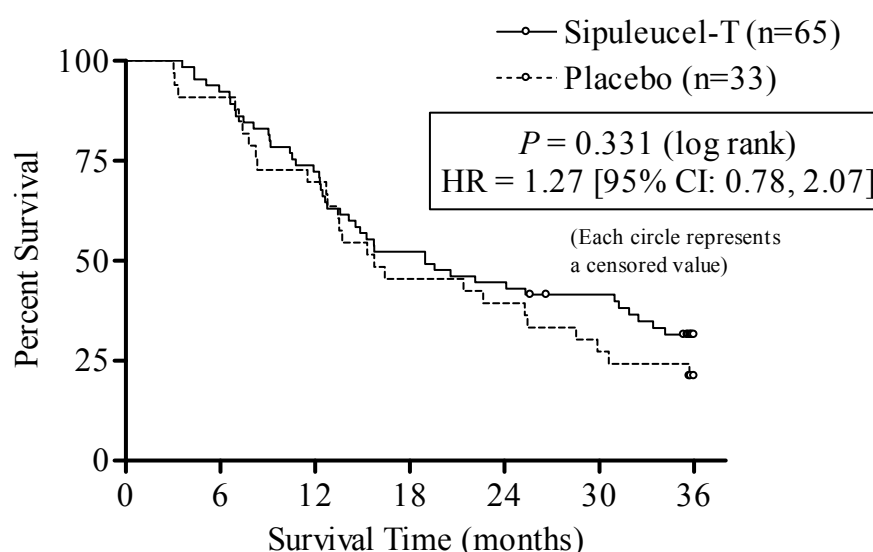
1.3.2.1 Overall Survival, Study 2

Ninety-eight patients with asymptomatic metastatic AIPC were randomized 2:1 to receive sipuleucel-T ($n = 65$) or placebo ($n = 35$). Study 2 demonstrated the following:

- A 21% reduction in the risk of death for patients treated with sipuleucel-T relative to placebo in the ITT population (HR = 1.27 [95% CI: 0.78, 2.07]; $P = 0.331$; [Figure 4](#)). All patients were followed until death or a pre-specified 36-month cut-off following randomization with the exception of 2 patients who were censored at 25.6 and 26.7 months.
- An increase in the percentage of patients alive at the pre-specified cut-off of 36 months following randomization, with 32% ($n = 21$) of patients treated with sipuleucel-T alive compared to 21% ($n = 7$) of patients treated with placebo.
- After adjusting for significant baseline prognostic factors (weight, PSA, LDH, lesion count, and localization of disease) identified in Study 1, the survival benefit in Study 2 increased. The HR was 1.92 ([95% CI: 1.09, 3.35]; $P = 0.023$).

- Adjustment for the use and timing of docetaxel demonstrated an HR of 1.50 ([95% CI: 0.90, 2.51]; $P = 0.121$).
- Prostate cancer specific survival demonstrated an HR of 1.35 ([95% CI: 0.08, 2.37]; $P = 0.287$).

Figure 4 Study 2 Overall Survival (Kaplan-Meier Method), ITT Population



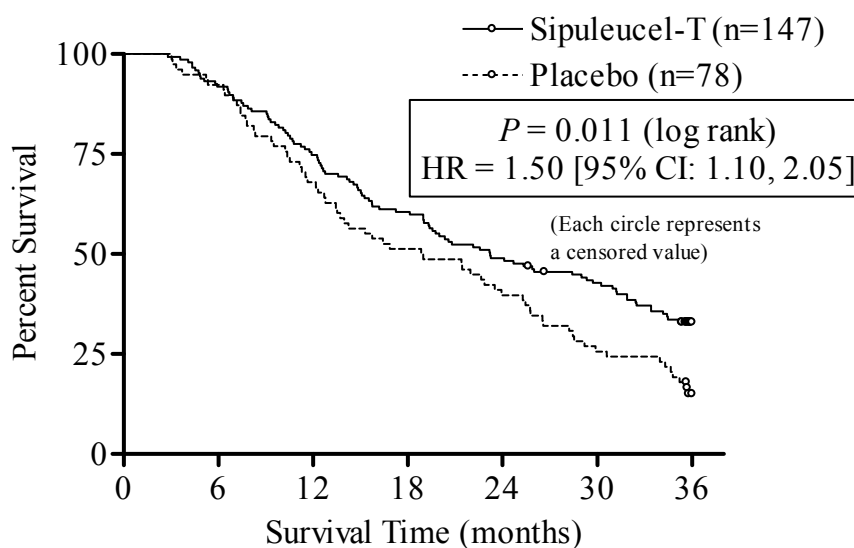
1.3.2.2 Overall Survival, Integrated Studies 1 and 2

An analysis integrating the efficacy data for Study 1 and Study 2 was conducted in order to provide another estimate of the treatment effect of sipuleucel-T. Two hundred twenty-five patients were randomized 2:1 to receive sipuleucel-T ($n = 147$) or placebo ($n = 78$). The integrated study results demonstrated the following:

- A 33% reduction in the risk of death for sipuleucel-T treated patients relative to placebo (HR = 1.50 [95% CI: 1.10, 2.05]; $P = 0.011$; [Figure 5](#)) in the ITT population.
- An increase in the percentage of patients alive at the pre-specified cut-off of 36 months following randomization, with 33% ($n = 49$) of patients treated with sipuleucel-T alive compared to 15% ($n = 12$) of patients treated with placebo.

- A robust survival benefit, as determined by multiple sensitivity analyses. After adjusting for significant baseline prognostic factors (weight, PSA, LDH, bone lesion count, and localization of disease), the HR was 1.86 ([95% CI: 1.31, 2.63]; $P < 0.001$).

Figure 5 Integrated Studies 1 and 2 Overall Survival (Kaplan-Meier Method), ITT Population

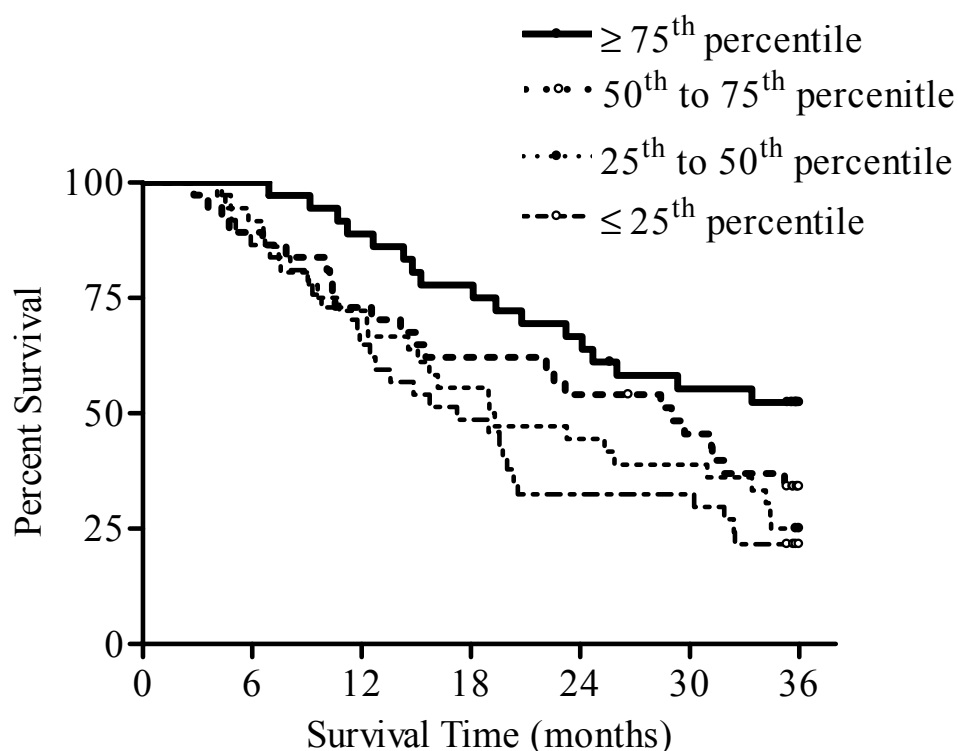


1.3.2.3 CD54 Upregulation Correlation with Overall Survival

Assessment of survival in the integrated Studies 1 and 2 and key product release specification parameters demonstrated a strong correlation between overall survival and product potency, cumulative CD54 upregulation ratio ($P = 0.009$), which persisted after adjustment for baseline prognostic factors (weight, PSA, LDH, bone lesion count, and localization of disease; $P = 0.022$).

The correlation between overall survival and cumulative CD54 upregulation is demonstrated in Figure 6, which shows the survival of patients by cumulative CD54 upregulation quartile. Patients with the greatest cumulative upregulation of CD54 (≥ 75 th percentile) had better survival than did patients in the lower quartiles. These results strongly suggest that sipuleucel-T is engaging the immune system and that key product quality attributes, including potency, correlate with clinical outcome.

Figure 6 Sipuleucel-T Survival by Cumulative CD54 Upregulation in Quartiles, Integrated Studies 1 and 2



1.3.3 Summary of Evidence of Clinical Efficacy

Multiple lines of evidence, including the overall survival and multiple sensitivity analyses from Study 1, the TTP results from Study 1, the supportive survival evidence from Study 2 and the integrated analysis of Studies 1 and 2, and the correlation between product potency and overall survival, strongly suggest that the overall survival results demonstrate a true clinical benefit, and are not the result of a Type 1 error (false positive).

1.4 Summary of Integrated Study 1 and Study 2 Safety Results

The safety population for Studies 1 and 2 includes 223 patients who underwent at least 1 leukapheresis. Adverse events (AEs) were collected through Week 16 (Day 112); following Week 16, AEs that were considered delayed treatment-related were collected, as well as all

deaths. These data were supplemented by data from the completed Phase I and Phase II studies, compassionate use trials, and ongoing Phase II and Phase III studies. The total safety population includes 669 patients who underwent at least 1 leukapheresis. Of these patients, approximately 478 patients received 1387 infusions of sipuleucel-T (numbers are estimates due to blinded data and include APC8026, a product similar to sipuleucel-T).

As described below, the most frequent events have been chills, pyrexia, and fatigue. These events were generally mild to moderate in severity, were typically treated on an outpatient basis, and resolved within a few days. Only 4 of the 223 patients in the Study 1 and Study 2 safety population did not receive all 3 infusions due to treatment-related AEs.

1.4.1 Adverse Events

Treatment with sipuleucel-T was well tolerated. The most common AEs were transient, not serious, of mild to moderate severity, and typically did not result in discontinuation of study treatment. In Studies 1 and 2, the most common AEs that occurred at a higher rate ($P \leq 0.05$) in patients treated with sipuleucel-T than in patients treated with placebo were chills, pyrexia, headache, asthenia, dyspnea, vomiting, and tremor ([Table 2](#)). These events were typically Grade 1 or 2 in severity, occurred soon after infusion, and were of short duration (1 to 2 days). A similar percentage of patients in each treatment group reported AEs that were severe or life threatening (Grade 3 or 4) or were reported as serious.

Table 2 Adverse Events Occurring in a Higher Percentage of Patients Treated with Sipuleucel-T versus Placebo ($P \leq 0.05^a$) in Studies 1 and 2, by Overall Occurrence and by Grade 3 and 4 AEs, Number (%) of Safety Population

Preferred Term	Any Grade ^b		Grade 3 or 4 ^b	
	Sipuleucel-T	Placebo	Sipuleucel-T	Placebo
	(n = 147) n (%)	(n = 76) n (%)	(n = 147) n (%)	(n = 76) n (%)
All Adverse Events ^c	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)
Pyrexia	47 (32.0)	5 (6.6)	3 (2.0)	0 (0.0)
Headache	28 (19.0)	5 (6.6)	2 (1.4)	0 (0.0)
Asthenia	21 (14.3)	3 (3.9)	0 (0.0)	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)
Tremor	13 (8.8)	0 (0.0)	0 (0.0)	0 (0.0)

^aBased on Fisher's exact test

^bSeverity Grade assessed by the Investigator using National Cancer Institute's Common Toxicity Criteria (version 2.0).

^cA treatment difference in the overall AEs was not observed between treatment arms ($P > 0.05$).

1.4.2 Adverse Drug Reactions

Adverse drug reactions (ADRs) to sipuleucel-T were defined based on 3 criteria: 1) greater incidence versus placebo; 2) temporal relationship to sipuleucel-T infusion; and 3) investigator causality assessment. Based on the review of the safety population of 669 patients, the following AEs appear to be potential ADRs to sipuleucel-T: chills, fatigue, asthenia, pyrexia, headache, nausea, vomiting, dyspnea, and tremor.

With the exception of asthenia and dyspnea, the majority of these potentially related ADRs occurred within 1 day of an infusion and occurred considerably less frequently after 14 or more days from last infusion.

The median duration of each of the ADRs was ≤ 2 days.

A small number of the ADRs were Grade 3 or greater in severity, were reported as serious adverse events (SAEs), or led to discontinuation of study treatment.

1.4.3 Clinically Important Events

Clinically important infusion-related AEs were defined as AEs occurring within 24 hours of an infusion of sipuleucel-T that were serious (i.e., AEs of any grade that required hospitalization) and/or Grade 3 or 4 in severity. Clinically important events occurred in 12 of the 147 (8.2%) patients who received sipuleucel-T in Study 1 and Study 2. These events required hospitalization in 5 of 147 patients (3.4%) who were treated with sipuleucel-T and led to discontinuation of therapy in 3 of 147 patients (2.0%). None of these events had a fatal outcome, and in general, the patients recovered within 24 hours and continued with additional sipuleucel-T infusions.

1.4.4 Deaths

There were no deaths attributed to the study product by the Investigators in the safety population of 669 patients. In the safety population of Studies 1 and 2, a total of 67% of patients treated with sipuleucel-T and 84% of patients treated with placebo died during the 3-year reporting period. The majority of the deaths were attributed to disease progression.

1.4.5 Serious Adverse Events

There was no difference in the incidence of SAEs between the sipuleucel-T and placebo arms in Studies 1 and 2 (23.8% versus 22.4%, respectively), and no SAEs (by preferred term) were reported in $\geq 5\%$ of patients in either treatment arm. The most common SAEs were chills, dehydration, dyspnea, urinary retention, hematuria, and pyrexia. Serious adverse events in 27 of 35 patients treated with sipuleucel-T who experienced an SAE (77.1%), and 13 of 17 patients treated with placebo who experienced an SAE (76.5%), were judged by the Investigator to be unrelated to study treatment, and most of these SAEs were related to disease progression or comorbidities seen in this patient population.

1.4.6 Additional Safety Observations

Some patients require placement of in-dwelling catheters to provide adequate venous access. Catheter-related infections (resulting from all types of venous catheters) occurred in 10 of the 223 patients (4.5%) in the safety population of Studies 1 and 2.

In Studies 1 and 2, there was no evidence that autoimmune events or second malignancies developed in a higher percentage of patients treated with sipuleucel-T versus placebo.

Cerebrovascular events were reviewed for all randomized and non-randomized studies. Based on all Phase III randomized trials, the overall incidence of cerebrovascular events in patients treated with sipuleucel-T and placebo was 3.9% and 2.6%, respectively (odds ratio [OR] = 1.5 [95% CI: 0.6, 3.9]; $P = 0.510$); the overall rate of deaths from cerebrovascular events was 1.5% versus 0.9%, respectively (OR = 1.77 [95% CI: 0.36, 8.57]; $P = 0.725$). Given the small number of cerebrovascular events in the randomized studies to date, the large p-values and wide confidence intervals for the odds ratios (which overlap 1), there is insufficient information to determine conclusively whether an association between sipuleucel-T and cerebrovascular events exists.

1.5 Risks and Benefits

The known and potential risks associated with treatment with sipuleucel-T include:

- Known treatment related risks with the most frequent being mild to moderate chills, fatigue, asthenia, fever, headache, nausea, vomiting, dyspnea, and tremor (which may be controlled with acetaminophen and diphenhydramine);
- Potential risks specific to the autologous nature of this product, including the need to place in-dwelling catheters to provide adequate venous access in some patients and the possibility that a patient may need to undergo additional leukapheresis procedures in the event that his leukapheresis or final product fails to meet release specifications or expiry periods; and
- A possible increased risk of cerebrovascular events.

These risks are manageable and balance favorably against the demonstrated benefits of treatment with sipuleucel-T. The benefits of treatment with sipuleucel-T include the following:

- Clinically significant prolongation of overall survival;
- Short treatment duration and high patient compliance rate;
- Favorable safety profile; and
- Treatment does not appear to preclude the use of other subsequent therapies such as chemotherapy.

Sipuleucel-T represents an important advance in the treatment of AIPC and, if approved, will provide physicians and patients with the option of a new therapy that is well tolerated and extends overall survival.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADPC	Androgen dependent prostate cancer
ADR	adverse drug reaction
AE	adverse event
AIPC	Androgen independent prostate cancer
alloMLR	allogeneic mixed lymphocyte reaction
APC	antigen presenting cell
BLA	Biologic License Application
CBER	Center for Biologics Evaluation and Research
CI	confidence interval
cpm	counts per minute
CTL	cytotoxic T lymphocyte
ECOG	Eastern Cooperative Oncology Group
ELISA	enzyme-linked immunosorbent assay
ELISPOT	enzyme-linked immunospot
FDA	Food and Drug Administration
FITC	fluorescein isothiocyanate
GM-CSF	granulocyte-macrophage colony-stimulating factor
HLA	human leukocyte antigen
HR	hazard ratio
IDMC	Independent Data Monitoring Committee
IL	interleukin
IND	Investigational New Drug
IFN γ	interferon-gamma
ITT	intent-to-treat
IV	intravenous
LDH	lactate dehydrogenase
ln	natural log
MHC	major histocompatibility complex
MMD	maximum manufacturable dose
NE	not estimable
NK	natural killer
OR	odds ratio
PA2024	recombinant fusion protein composed of PAP linked to GM-CSF
PAP	prostatic acid phosphatase
PBMC	peripheral blood mononuclear cell
PSA	prostate-specific antigen
PSADT	prostate-specific antigen doubling time
RECIST	response evaluation criteria in solid tumors

Abbreviation	Definition
SAE	serious adverse event
s.c.	subcutaneous
SEM	standard error of the mean
SI	stimulation index
TDRP	time to disease related pain
TNC	total nucleated cell
TNF α	tumor necrosis factor alpha
TTP	time to disease progression

2.0 INTRODUCTION

Sipuleucel-T is therapy which belongs to a new class of treatments designed to stimulate a patient's own immune system against cancer. Sipuleucel-T, also referred to as APC8015, is an autologous active cellular immunotherapy product aimed at stimulating an immune response against prostate cancer. It consists of autologous peripheral blood mononuclear cells (PBMCs), including antigen presenting cells (APCs), that have been activated in vitro with a recombinant fusion protein. The recombinant fusion protein, PA2024, is composed of prostatic acid phosphatase (PAP), an antigen highly expressed in prostate adenocarcinoma, linked to granulocyte-macrophage colony-stimulating factor (GM-CSF), an immune cell activator.

During the manufacture of sipuleucel-T, the cellular composition remains consistent throughout the process, but the APCs become activated. APC activation is defined by the upregulation of cell surface molecules like CD54, human leukocyte antigen (HLA)-DR, CD86 and CD40. The upregulation of CD54 is one means by which the potency of each lot of sipuleucel-T is determined. The cumulative upregulation of CD54 correlates with survival.

2.1 Proposed Label Indication and Treatment

The proposed label indication is "Sipuleucel-T is indicated for the treatment of men with asymptomatic metastatic androgen independent prostate cancer."

The recommended course of therapy for sipuleucel-T is 3 doses, given by intravenous (IV) infusion at approximately 2-week intervals. Each dose of sipuleucel-T is preceded by a standard leukapheresis procedure approximately 2 to 4 days prior to the infusion date. Each dose must be administered to the patient from whom the cells were obtained.

2.2 Clinical Context and Endpoints in Advanced Prostate Cancer

2.2.1 Clinical Context

Prostate cancer is the most common solid tumor malignancy in men in the United States, and it is expected to account for over 218,890 new cases and approximately 27,050 deaths in 2007 (Jemal, 2007). While primary therapy (surgery, radiation therapy, brachytherapy, cryotherapy)

usually controls the disease, approximately 20% to 40% of prostate cancer patients will eventually experience disease recurrence, typically with elevated prostate-specific antigen (PSA) levels ([Ward, 2005](#)). For those men whose disease recurs, androgen deprivation is the standard treatment, resulting in temporary tumor control or regression in 80% to 85% of patients ([Crawford, 1989](#); [Scher, 1993](#); [Small, 1995](#); [Schellhammer, 1997](#)).

Despite hormonal therapy, virtually all of these patients will progress and become refractory to hormone therapy, a state also known as androgen independent prostate cancer (AIPC). Management of patients with advanced AIPC remains a significant clinical challenge as almost all of these men die from their disease and current treatment options are limited.

The numerous trials conducted in men with metastatic AIPC over the past several decades have led to only a limited number of Food and Drug Administration (FDA) approved therapies. Mitoxantrone (Novantrone[®], OSI Pharmaceuticals, Inc.) in combination with prednisone was approved by FDA based on improved palliation in patients with symptomatic disease compared to prednisone alone. Zoledronic acid (Zometa[®], Novartis Pharma AG) was approved by FDA based on a reduction in skeletal related events. Docetaxel (Taxotere[®], Sanofi-Aventis) in combination with prednisone is the only FDA approved treatment regimen that has been shown to confer a survival advantage (2.5 months) in men with metastatic AIPC. Treatment-related toxicities associated with docetaxel may include Grade 3 or 4 neutropenia, infection, anemia, and neuropathy ([Docetaxel Product Label, 2005](#)). These risks may outweigh the benefits for some patients, reducing acceptance and compliance. There remains a clear need for well tolerated therapies that benefit patients with advanced AIPC, particularly those with no cancer-related pain, many of whom elect not to pursue chemotherapy ([Kirk, 2006](#)).

2.2.2 Endpoints in Advanced Prostate Cancer

In most oncologic diseases, tumor response has proven a valuable surrogate measure with which to assess the efficacy of new agents. In advanced prostate cancer, where the disease occurs predominantly in bone, bidimensionally measurable disease is not present in the majority of patients, so that the standard tumor response criteria, such as response evaluation criteria in solid tumors (RECIST), are not applicable.

Serum PSA is a biomarker that is widely used to follow the course of the disease clinically, but its use as a surrogate endpoint remains controversial.

Time to disease progression (TTP) or progression-free survival is frequently accepted in oncology as an appropriate surrogate measure for overall survival. Time to progression is more challenging in advanced prostate cancer because of the reliance on bone scans, which may be non-specific or confounded by tumor response flares that may be difficult to distinguish from disease progression. In a randomized trial comparing docetaxel and estramustine with mitoxantrone and prednisone, an improvement in progression-free survival was observed, which translated to an overall survival benefit (Petrylak, 2004), but this was not reported in the Tax327 registration trial comparing docetaxel to mitoxantrone and prednisone, where there was a high degree of censoring for this endpoint (Dagher, 2004). Given the rapid progression of disease as measured by bone scan in advanced prostate cancer, the TTP endpoint becomes particularly challenging for non-cytotoxic therapies, such as immunotherapy, which may have a delayed onset of action.

Overall survival remains the most compelling outcome in advanced prostate cancer and in oncology trials in general, based on its objectivity and clinical relevance. However, despite decades of investigation, it has been difficult to achieve in advanced prostate cancer, with docetaxel being the only agent to date demonstrating a survival benefit in this population. The approval of docetaxel in AIPC was therefore a landmark event for the field. The importance of demonstrating a survival benefit was stressed by FDA Oncologic Drugs Advisory Committee panel that met in March 2005 to discuss endpoints relevant to clinical trials in prostate cancer (<http://www.fda.gov/ohrms/dockets/ac/cder05.html#OncologicDrugs>). While there was considerable debate regarding surrogate endpoints (particularly in earlier stages of the disease), a clear consensus emerged regarding endpoints in advanced/metastatic disease: survival is the 'gold standard' endpoint.

A clinically significant improvement in overall survival is the basis of the Biologic License Application (BLA) filing for sipuleucel-T.

3.0 PROGRAM DESIGN AND REGULATORY HISTORY

The Investigational New Drug (IND) application for sipuleucel-T was submitted in November 1996 for the treatment of prostate cancer. A summary of all clinical trials of sipuleucel-T to date is provided in [Appendix 1](#). Following completion of the first Phase I and II studies (Protocols ACT 9610 and ACT 9702), several end-of-Phase II meetings were held with the FDA's Center for Biologics Evaluation and Research (CBER) in 1998 and 1999 to discuss the proposed Phase III development plan for sipuleucel-T. These discussions led to the design of the Phase III program to evaluate the safety and effectiveness of sipuleucel-T in men with asymptomatic metastatic AIPC. An overview of the clinical development program for sipuleucel-T is provided in Figure 7.

Figure 7 Clinical Development Program for Sipuleucel-T

Phase I & II Studies	Phase III Completed Studies	Phase III Ongoing Studies
<u>Androgen Independent Prostate Cancer</u> Study ACT 9610 Study ACT 9702 Study D9801 Study D9903 Study PB01	<u>Androgen Independent Prostate Cancer</u> Study 1 (Protocol D9901) Study 2 (Protocol D9902A)	<u>Androgen Independent Prostate Cancer</u> Study 3 (Protocol D9902B) <u>Androgen Dependent Prostate Cancer</u> Study P-11

The target patient population of asymptomatic metastatic AIPC represented an unmet medical need, since there were no approved treatment options shown to delay progression or prolong survival in this setting. Standard chemotherapies available at start of Studies 1 and 2 were palliative and none had been shown to prolong survival in AIPC. The results of Dendreon's Phase I and II studies suggested that, compared to historical controls, disease progression was delayed following treatment with sipuleucel-T. For these reasons, the primary efficacy measure

proposed to the Agency for the Phase III studies was a delay in TTP for patients treated with sipuleucel-T compared to a placebo control.

The Phase III program, originally intended to support licensure, consisted of 2 multicenter, randomized, double blind, placebo-controlled trials comparing sipuleucel-T to a control infusion (autologous PBMCs without antigen and activation). The design of the placebo required that all patients undergo a leukapheresis procedure to ensure that the double blind nature of the study remain intact. The studies were designated D9901 (Study 1) and D9902 (Study 2). The sample size of each study was calculated to provide 80% power to detect an increase in the median TTP from 4 months in the placebo arm to 7.7 months in the sipuleucel-T arm (a hazard ratio [HR] of 1.925), with a 2-sided 5% level of significance. In both trials, the original protocols and statistical analysis plans specified that patients were to be followed until death or until 36 months from the time of randomization, whichever occurred first.

A Phase II salvage (or “crossover”) study was included in the design of the Phase III studies, so patients who were randomized to receive placebo could be given the option to receive “salvage” therapy with APC8015F (a product similar to sipuleucel-T) after disease progression. This design feature was included to address concerns raised by clinical investigators regarding accrual to a placebo-controlled study. The “F” indicates that the infusion product was prepared using a portion of the leukapheresis cells that were frozen and stored for potential use in the salvage study.

Enrollment to Studies 1 and 2 began in January 2000 and May 2000, respectively. Enrollment to Study 1 was completed in October 2001 at 127 patients and the study was subsequently analyzed. At that time, the results of this analysis of the Study 1 intent-to-treat (ITT) population demonstrated a trend in delaying TTP that did not achieve statistical significance. This initial result for TTP in Study 1 suggested a lack of clear utility for the TTP endpoint and that Study 2 was unlikely to meet its primary endpoint. Therefore, enrollment in Study 2 was stopped early. All patients in both Studies 1 and 2 continued to be followed for overall survival. In 2003, Dendreon and FDA discussed the results of Study 1 and, under a Special Protocol Assessment and Agreement, designed a new study (Study D9902B, also referred to as Study 3) to continue the investigation of sipuleucel-T in asymptomatic, metastatic AIPC in a randomized, double

blind, placebo-controlled study. Enrollment is ongoing in Study 3, and the final survival analysis is anticipated in 2010.

In 2004, the 36 month ITT analysis of survival in Study 1 demonstrated a statistically persuasive and clinically meaningful improvement in overall survival for patients randomized to sipuleucel-T compared to those randomized to placebo. The overall survival results from Study 2 showed a trend in favor of sipuleucel-T, although the p-value associated with the treatment effect was greater than 0.05.

Dendreon is seeking licensure of sipuleucel-T for the treatment of men with asymptomatic metastatic AIPC. Substantial evidence of efficacy to form the basis for licensure is provided by Study 1, a well conducted, randomized, double blind, multicenter, placebo-controlled trial, which demonstrated a clinically meaningful and robust improvement in overall survival, as well as a strong trend toward a delay in TTP based on all randomized patients. In addition, results from Study 2 revealed a trend toward improved survival. Further supportive evidence is provided by a strong correlation between overall survival and cumulative CD54 upregulation (an indicator of APC activation), which is a component of product potency.

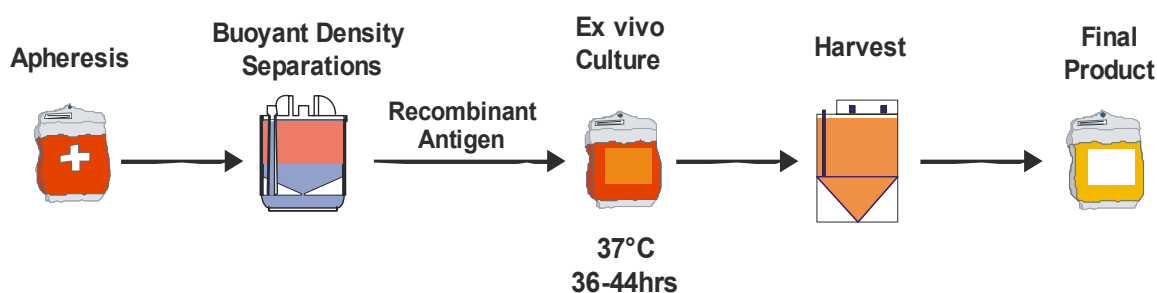
Though survival was not pre-specified as the primary endpoint in either study, it is well accepted that survival is the most objective and meaningful measure of clinical benefit in oncology trials and the study results should therefore be considered in this context. The survival results from Study 1 are further supported by the delay in TTP and other related endpoints in Study 1 as well as by supportive evidence from the correlation between overall survival and product specific attributes, such as product potency and dose. The survival benefit along with the highly favorable safety profile make sipuleucel-T an appealing treatment option for patients with metastatic AIPC.

4.0 PRODUCT DESCRIPTION AND CHARACTERIZATION

Sipuleucel-T consists of a patient's own PBMCs, including APCs that have been activated ex vivo with a recombinant fusion protein, PA2024. This protein is composed of PAP, an antigen expressed in prostate adenocarcinoma, linked to GM-CSF, an immune cell activator.

Each course of sipuleucel-T treatment consists of 3 infusions, prepared and administered at approximately 2-week intervals. For each dose, the patient undergoes a standard 1.5 to 2.0 L blood volume leukapheresis procedure to collect PBMCs. The cells are shipped to Dendreon's manufacturing facility, where they are aseptically processed and cultured in the presence of PA2024, the recombinant antigen, then washed to remove excess antigen and residual process solutions (Figure 8). The ex vivo culture yields activated, antigen-loaded APCs capable of presenting PAP epitopes to T cells.

Figure 8 Sipuleucel-T Process Overview



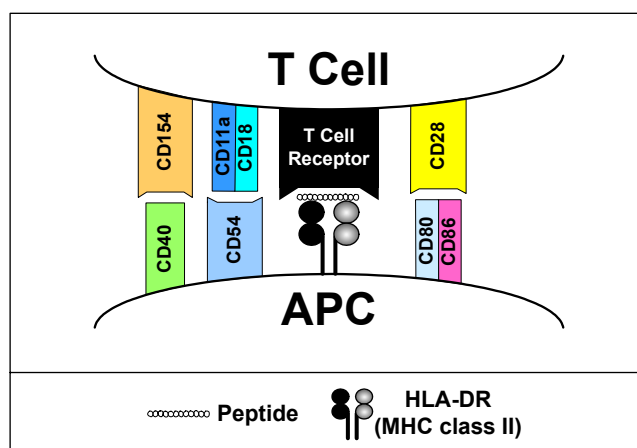
The manufacturing process is robust, consistently yielding a final product that meets quality, purity, safety, and potency specifications. The sipuleucel-T product is shipped to the patient's physician for infusion. Because each dose is prepared from a fresh leukapheresis, the second and third doses are prepared using cells from the patient who has already been treated with sipuleucel-T.

Sipuleucel-T has been extensively characterized. Both cell phenotype and cell activation studies have contributed to the characterization studies. The leukapheresis starting material and the final product contain a mixture of cells, including T cells, B cells, natural killer (NK) cells, and APCs. Characterization studies have shown that the APC population contains important biological activity.

4.1 APCs in Sipuleucel-T Express CD54

Antigen-specific responses are mediated by APCs, which stimulate T cells and cause antigen-specific T cell expansion. T cell stimulation requires that the APCs take up and process antigen, then present antigen-derived peptides in the context of surface major histocompatibility complex (MHC) molecules. Stimulation is further mediated by interactions between APC surface costimulatory molecules and their respective T cell ligands. These interactions at the interface between APCs and T cells form the “immunological synapse,” as depicted in Figure 9.

Figure 9 Simplified Schematic of the Immune Synapse



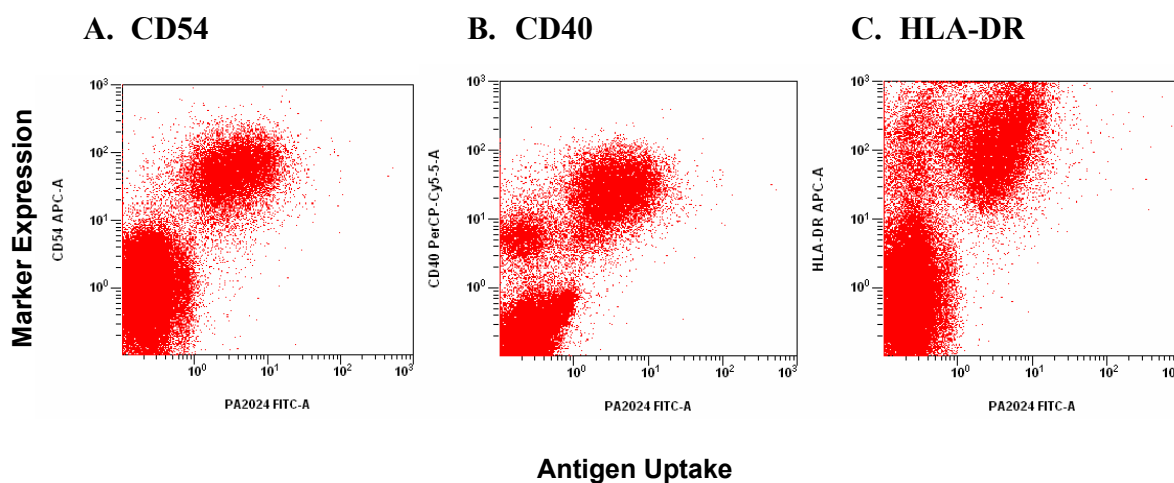
One of these immune synapse proteins is CD54 (also known as ICAM-1), which interacts with LFA-1 (CD11a/CD18) on T cells. In addition to increasing the avidity of the cell-to-cell contact, this interaction provides a costimulatory signal to T cells. The following experiments demonstrated that the CD54⁺ cell population contains the antigen uptake and presentation activity and the costimulatory activity in sipuleucel-T. Thus, CD54⁺ expression has been used to identify the APCs in sipuleucel-T.

4.1.1 CD54⁺ Cells Incorporate PA2024

To determine which cells in sipuleucel-T take up the PA2024 antigen, manufacturing was performed according to the standard procedure, but the ex-vivo culture was spiked with fluorescently-labeled PA2024 (PA2024-fluorescein isothiocyanate [FITC]). The product cells

were then stained with antibodies against cell surface molecules, and analyzed by flow cytometry. Figure 10 shows that PA2024 uptake (shown on the X axis) correlates closely with CD54 expression (shown on the Y axis of Panel A). While all cells that take up PA2024 also express CD40 and HLA-DR, there are populations of CD40⁺ and HLA-DR⁺ cells that do not incorporate PA2024 (Panels B and C). Thus, the superior correlation of CD54 expression with antigen uptake contributed to the selection of CD54 as the marker for APC activity in sipuleucel-T.

Figure 10 Antigen Uptake and Expression of Immune Synapse Proteins



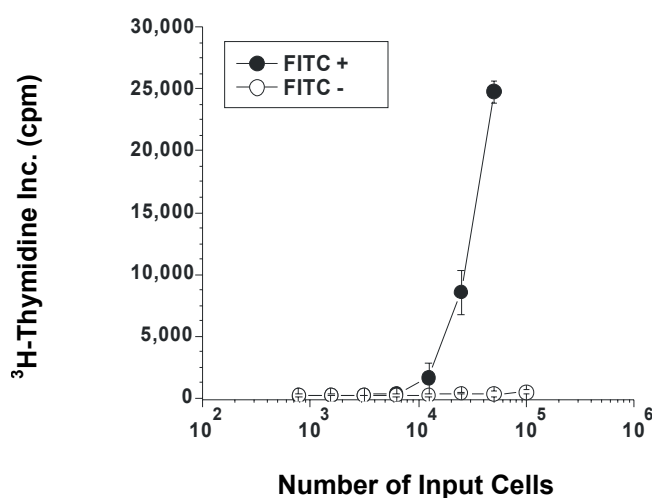
4.1.2 PAP Epitope Presentation by Sipuleucel-T

To measure the presentation of PAP epitopes to T cells, Dendreon developed MHC class II-restricted, PAP-specific, CD4⁺ T cell hybridomas specific for APCs presenting PAP peptides in the context of HLA-DRβ1. The T cell hybridomas produce interleukin (IL)-2 in response to PAP-loaded APCs. The magnitude of the stimulation can be quantified by measuring IL-2 production using proliferation of an IL-2 dependent cell line (as measured by incorporation of ³H-thymidine) or using an IL-2 enzyme enzyme-linked immunosorbent assay (ELISA).

In order to evaluate the correlation between PA2024 uptake and antigen presentation activity, sipuleucel-T was manufactured using PA2024 spiked with FITC-labeled PA2024. Cells that took up PA2024 became FITC⁺ and detectable by flow cytometry. Product cells were sorted into

FITC⁺ and FITC⁻ populations by fluorescence-activated cell sorting, and then assayed using the PAP-specific antigen presentation assay. Figure 11 shows that the FITC-labeled cells are able to process and present antigen to the T cell hybridomas. The FITC⁻ population lacks PAP antigen presentation activity, demonstrating that antigen uptake is required for activation of PAP-specific T cells.

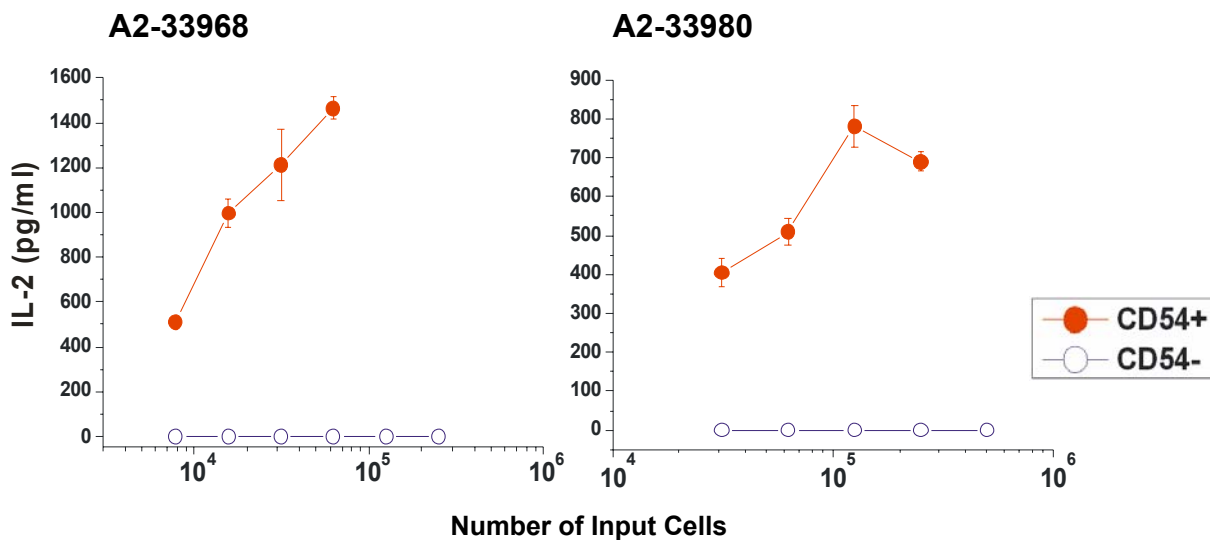
Figure 11 PA2024 Uptake is required for PAP-specific T cell Stimulation



4.1.3 PAP Epitope Presentation in Sipuleucel-T Resides in CD54⁺ Cells

As shown in Figure 10, CD54 expression correlates with antigen uptake. To evaluate the correlation between CD54 expression and antigen presentation activity, after culture with PA2024, cells were sorted into CD54⁺ and CD54⁻ populations by fluorescence-activated cell sorting and then assayed using the PAP-specific antigen presentation assay via a PAP-specific T cell hybridoma. Figure 12 shows that the CD54⁺ cell population contains all of the antigen presentation activity in sipuleucel-T (results from 2 different donors are shown).

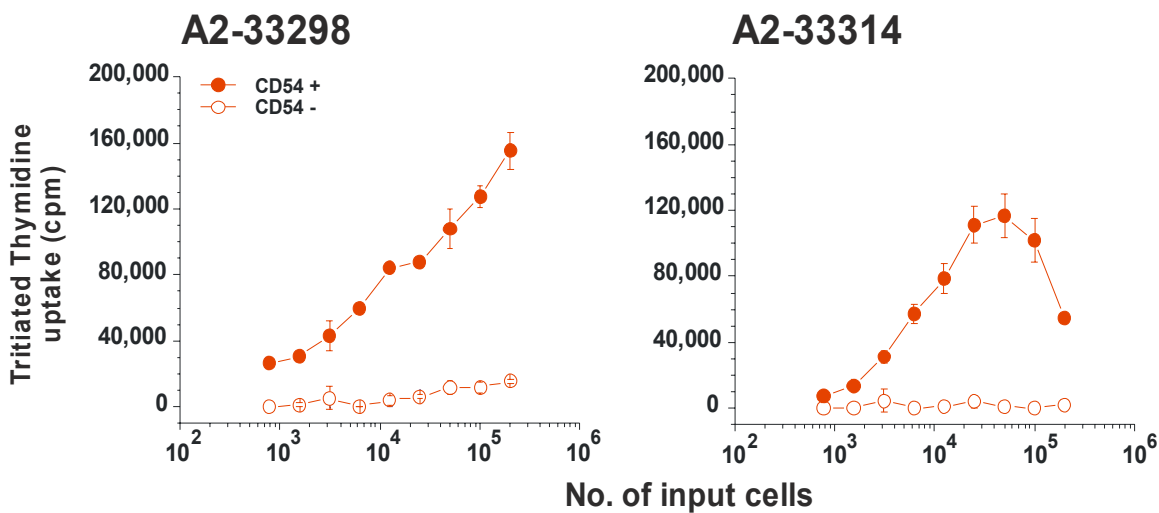
Figure 12 $CD54^+$ Cells Stimulate PAP-specific T Cells



4.1.4 Costimulatory Activity of Sipuleucel-T Resides in $CD54^+$ Cells

T cell stimulatory activity can be measured using the allogeneic mixed lymphocyte reaction (alloMLR) assay. This assay evaluates the ability of APCs to activate allogeneic T cells, giving a non-antigen-specific measure of costimulatory ability. Cells were sorted into $CD54^+$ and $CD54^-$ populations by fluorescence-activated cell sorting and then assayed using the alloMLR assay. Figure 13 shows that the $CD54^+$ cell population contains all of the costimulatory activity in sipuleucel-T (results from 2 different donors are shown).

Figure 13 $CD54^+$ Cells Stimulate Allogeneic T Cells



Because the CD54⁺ cell population contains the ability to take up and present antigen, as well as the costimulatory activity in sipuleucel-T, CD54 expression is used to identify the APCs in sipuleucel-T. Most of these APCs also express CD14, and are thus monocyte-derived APCs. A small number of blood derived dendritic cells (lineage negative, HLA-DR⁺ cells) are also found in the CD54⁺ cell population.

4.2 Antigen Presenting Cells in Sipuleucel-T Increase CD54 Expression on Activation

Compared to quiescent APCs, activated APCs have an enhanced capacity to stimulate T cells. One hallmark of APC activation is the increased expression, or upregulation, of molecules that play a role in the immunological synapse. This upregulation serves to strengthen the contact between the 2 cell types and provides costimulatory signals in addition to the primary signals from the MHC-peptide-T cell receptor complex. The following experiments demonstrate that CD54 expression levels 1) increase during ex vivo culture and 2) correlate with T cell stimulatory activity in sipuleucel-T. CD54 upregulation is thus used to assess APC activation in sipuleucel-T.

4.2.1 CD54 is Upregulated during Ex Vivo Culture

During ex vivo culture with PA2024, proteins known to play a role in the immunological synapse are upregulated, as shown in [Figure 14](#) and [Figure 15](#). In the histograms presented in [Figure 14](#), the shaded peaks show staining of ungated cells by fluorescently-labeled antibodies to HLA-DR, CD54, CD40, and CD86. The unshaded peaks show nonspecific staining levels obtained with fluorescently-labeled, isotype matched, control antibodies. After ex vivo culture, the specifically-stained peaks shift to the right, showing an increase in the expression of each of these markers. In particular, the CD54⁺ population is readily distinguished from the nonspecifically-stained population.

Figure 14 **Upregulation of Immune Synapse Proteins after Culture with PA2024**

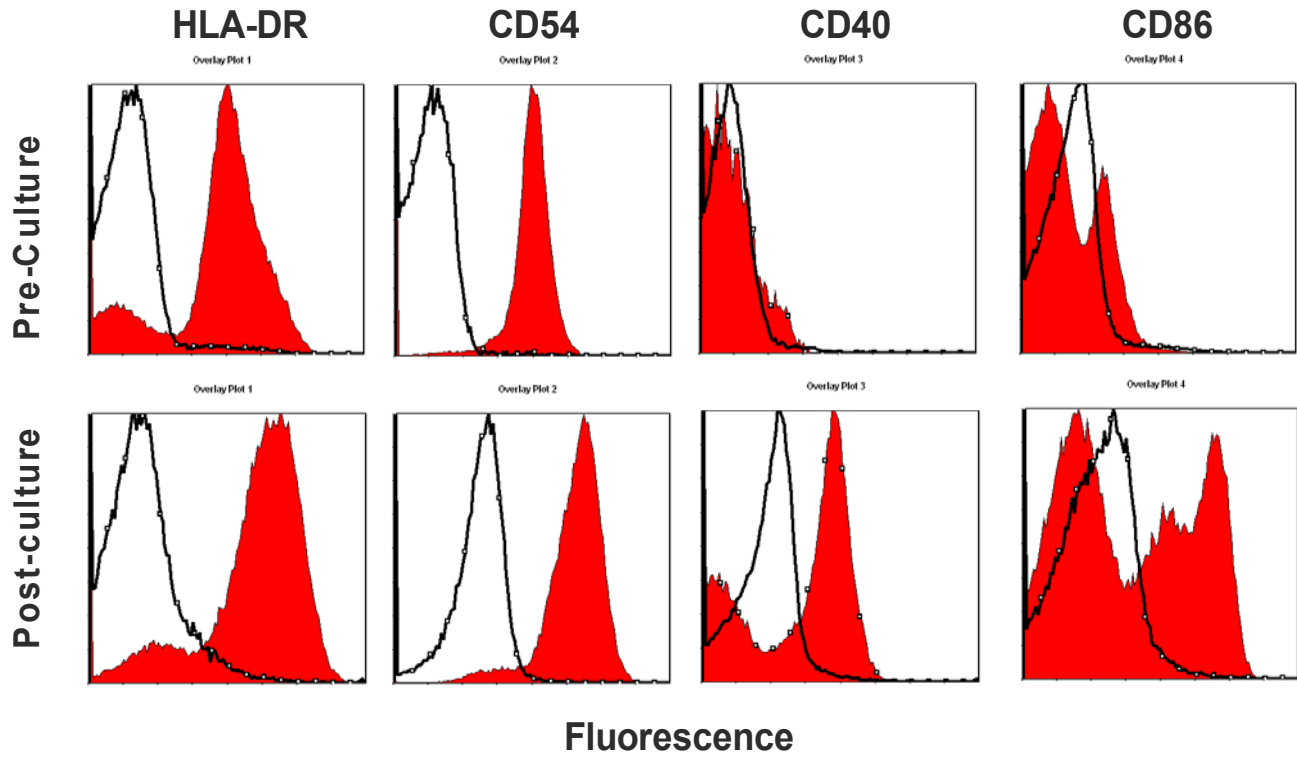
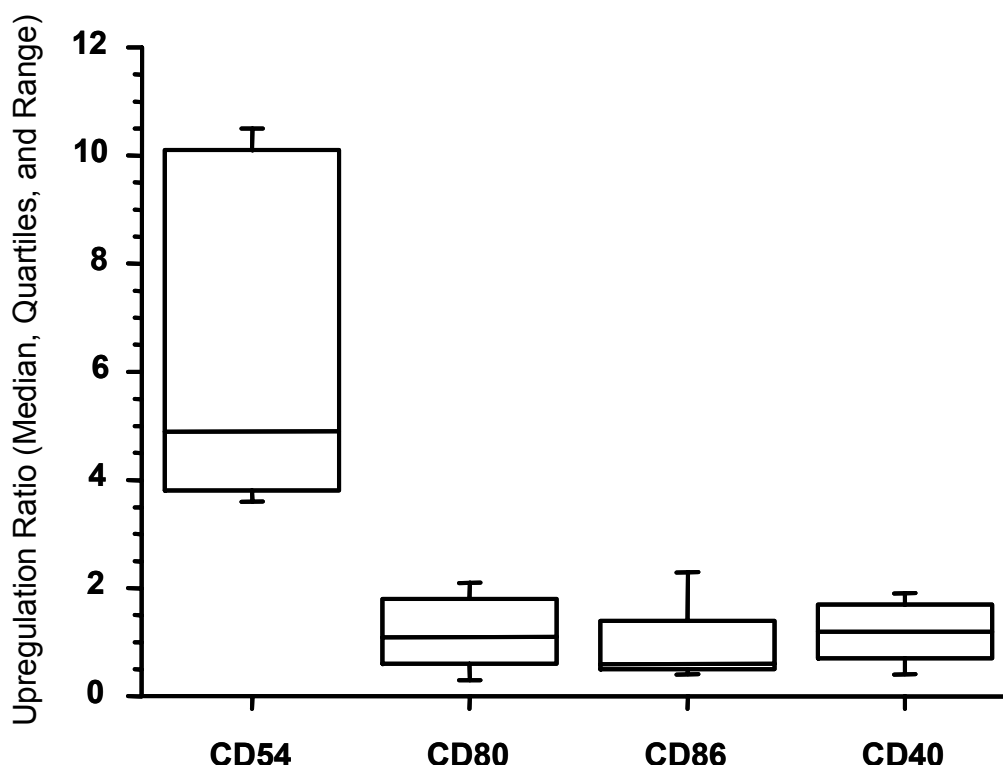


Figure 15 Fold Upregulation of Costimulatory Molecules Following Incubation with PA2024

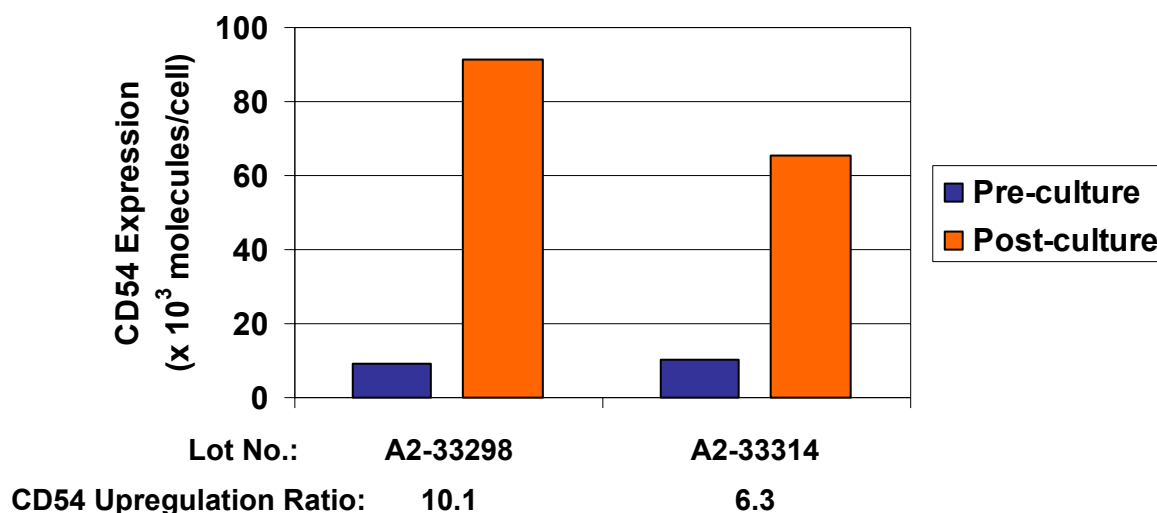


Of the markers evaluated, CD54 is most consistently upregulated on APCs following culture with PA2024 (Figure 15). Because the CD54⁺ population is distinct from the CD54⁻ population, increases in CD54 expression during ex vivo culture are readily quantified by flow cytometry. For product potency testing, samples taken before and after ex vivo culture are assayed by flow cytometry to determine the average CD54 expression by large CD54⁺ cells. CD54 upregulation is calculated as the ratio of the post-culture CD54 expression level to the pre-culture CD54 expression level:

$$\text{CD54 Upregulation Ratio} = \frac{\text{Mean No. of CD54 Molecules Expressed on Gated Cells Post-culture}}{\text{Mean No. of CD54 Molecules Expressed on Gated Cells Pre-culture}}$$

Figure 16 illustrates the CD54 upregulation results for the 2 lots of sipuleucel-T shown in Figure 13. The mean numbers of CD54 molecules expressed on gated cells pre- and post-culture are shown along with the resultant CD54 upregulation ratio (below the figure).

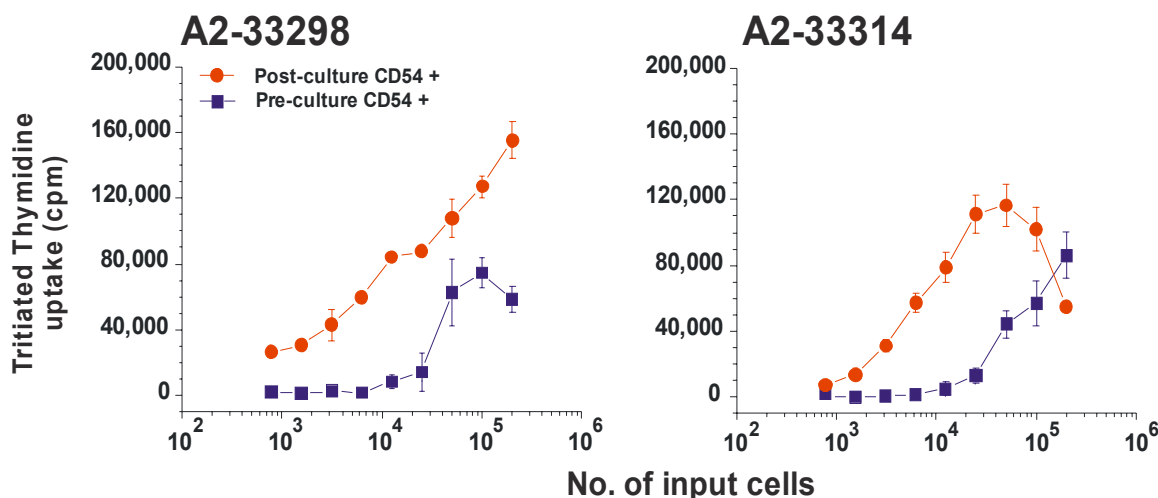
Figure 16 CD54 is Upregulated during Ex Vivo Culture



4.2.2 CD54 Upregulation Correlates with Costimulatory Activity

Antigen presenting cell activation results in increased T cell stimulatory activity, and these increases can be measured using the alloMLR assay. To functionally evaluate APC activation, the 2 lots of sipuleucel-T shown above and in Figure 13 were assayed for costimulatory activity before and after ex vivo culture. As shown in Figure 17, costimulatory activity in the CD54⁺ population is considerably enhanced by ex vivo culture with PA2024. Costimulatory activity was not observed in the CD54⁻ population, either before or after culture.

Figure 17 Allogeneic T cell Stimulation Increases During Ex Vivo Culture



These results show that APCs in sipuleucel-T are activated by the ex vivo culture step and the activated APCs have increased expression of surface CD54. Furthermore, the data highlight the fact that CD54⁺ cells have antigen presenting activity, as well as costimulatory activity. For these reasons, APC activation in sipuleucel-T can be assessed by measuring the increase in CD54 expression.

4.3 CD54 Expression Indicates Sipuleucel-T Potency

Per 21 CFR 600.3(s), potency is the quantitative measure of in vitro biological activity, which is the specific ability or capacity of a drug substance or product to achieve a defined biological effect. While potency specifications ensure a consistent product, potency is not required to correlate with or predict efficacy, which is the in vivo measure of a product's clinical activity. The biologic effect of sipuleucel-T is to activate the immune system of prostate cancer patients. In vitro models of this function include the alloMLR assay, which measures costimulatory activity, and the PAP-specific antigen presentation assay, which measures antigen uptake, processing, and presentation in an MHC-restricted manner. These in vitro models mimic the biologic functions of sipuleucel-T and would therefore be relevant assays for characterizing product potency.

These in vitro T cell assays take several days to complete, which is too long to satisfy the timeframe for product release testing. Furthermore, the T cell hybridomas that are the basis for

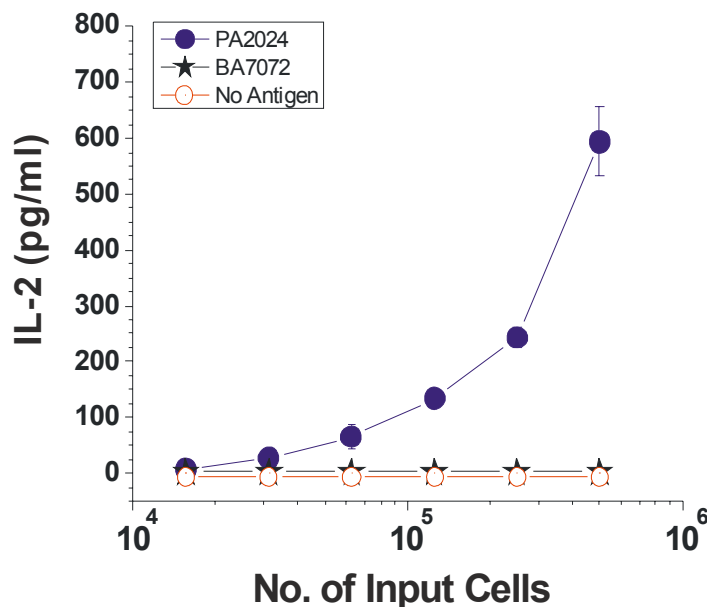
the PAP-specific antigen presentation assay will only respond to HLA-DR β 1⁺ APCs and are not applicable to other MHC haplotypes. Since CD54 expression on APCs correlates with alloMLR costimulatory activity and PAP-specific antigen presentation activity, CD54 expression on APCs is used as a surrogate measure of product potency.

Flow cytometry is used in two ways to assay for CD54 expression on APCs in sipuleucel-T product potency release testing: 1) to quantify the number of CD54⁺ APCs; and 2) to measure the upregulation of CD54 expression on APCs. These measures ensure an adequate number of APCs and ensure that the APCs are activated.

4.4 The Roles of PAP and GM-CSF in Sipuleucel-T

PA2024 is composed of PAP fused to GM-CSF, a hematopoietic growth factor that enhances the activation of APCs and promotes cell viability in culture. The PAP-specific antigen presentation assay shows that ex vivo culture with PA2024 is absolutely required to generate APCs with PAP antigen presentation activity. [Figure 18](#) shows that culture with BA7072 (a recombinant protein consisting of HER2/neu sequences fused to GM-CSF) does not demonstrate PAP antigen presentation activity. Thus, the biologic function of sipuleucel-T requires the PAP epitopes supplied by incubation with PA2024. GM-CSF alone is not sufficient to produce a product that is able to present PAP epitopes to T cells.

Figure 18 PAP Antigen Presentation Requires PAP Epitopes Supplied by PA2024



4.5 Changes in Sipuleucel-T over Successive Treatments

Each dose of sipuleucel-T is prepared from a fresh leukapheresis, so immune responses to the first dose may be observed in the cells used to prepare the second and third doses. Changes in the properties of these cells over successive treatments suggest that the first dose primes and activates the immune system.

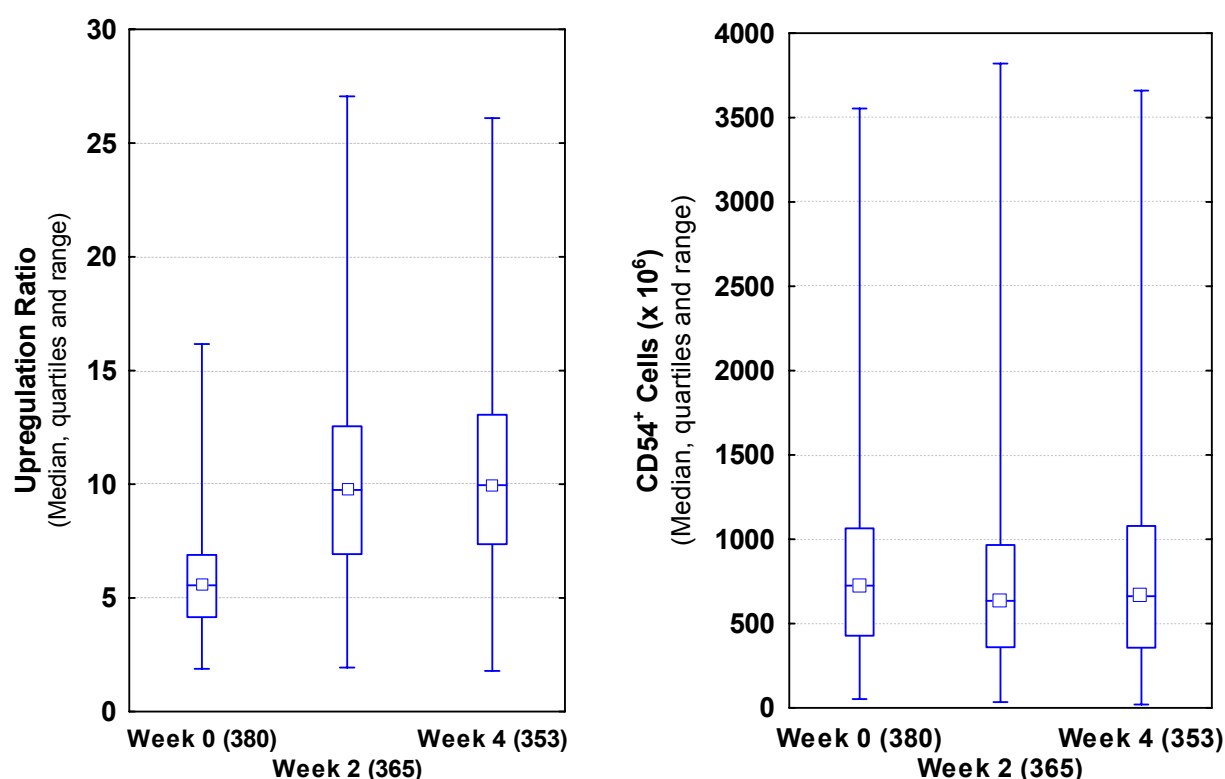
4.5.1 Antigen Presenting Cell Activation Increases after Treatment

Figure 19 compares CD54 upregulation ratio and total CD54⁺ cell number in Week 0, Week 2, and Week 4 products prepared for patients. (In this figure, the number of values in each group is shown in parentheses. Because some patients did not receive a full course of treatment, the number of available values varies by treatment week. Lots are representative of products from Phase III studies.) The median CD54 upregulation ratio increased at Weeks 2 and 4 after the initial infusion of sipuleucel-T. The difference in the median CD54 upregulation ratio between Week 0 and Week 2 and between Week 0 and Week 4 was significant at the $P < 0.0001$ level. While this increase is clear in the aggregate data, an individual patient may not have demonstrated an increase over the course of his treatment. These data support the hypothesis

that the first dose activates the immune response, resulting in changes in the phenotypic characteristics of sipuleucel-T at Weeks 2 and 4.

Unlike upregulation ratio, the number of CD54⁺ cells was similar for all treatment weeks. Priming the immune response with the Week 0 dose would not necessarily be expected to result in an increase in the number of APCs.

Figure 19 Changes with Treatment in Sipuleucel-T Potency Measures

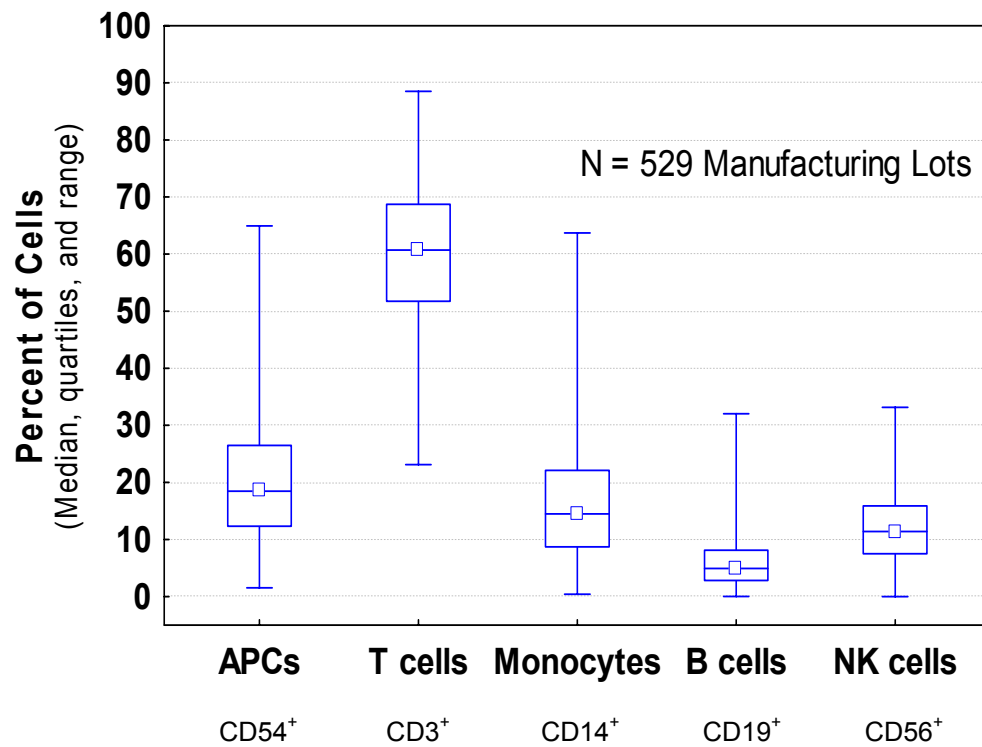


4.5.2 Cell Composition of Sipuleucel-T

In addition to APCs, sipuleucel-T contains other cell types, including T cells, B cells, and NK cells. [Figure 20](#) shows the median, quartiles, and range of percentages of these cell types in 529 lots of sipuleucel-T manufactured for Phase III clinical studies. These results show that T cells, identified by the CD3 cell surface marker, are the predominant cell type. The second most abundant cell type is APCs, which are identified by the cell surface marker, CD54. Most of

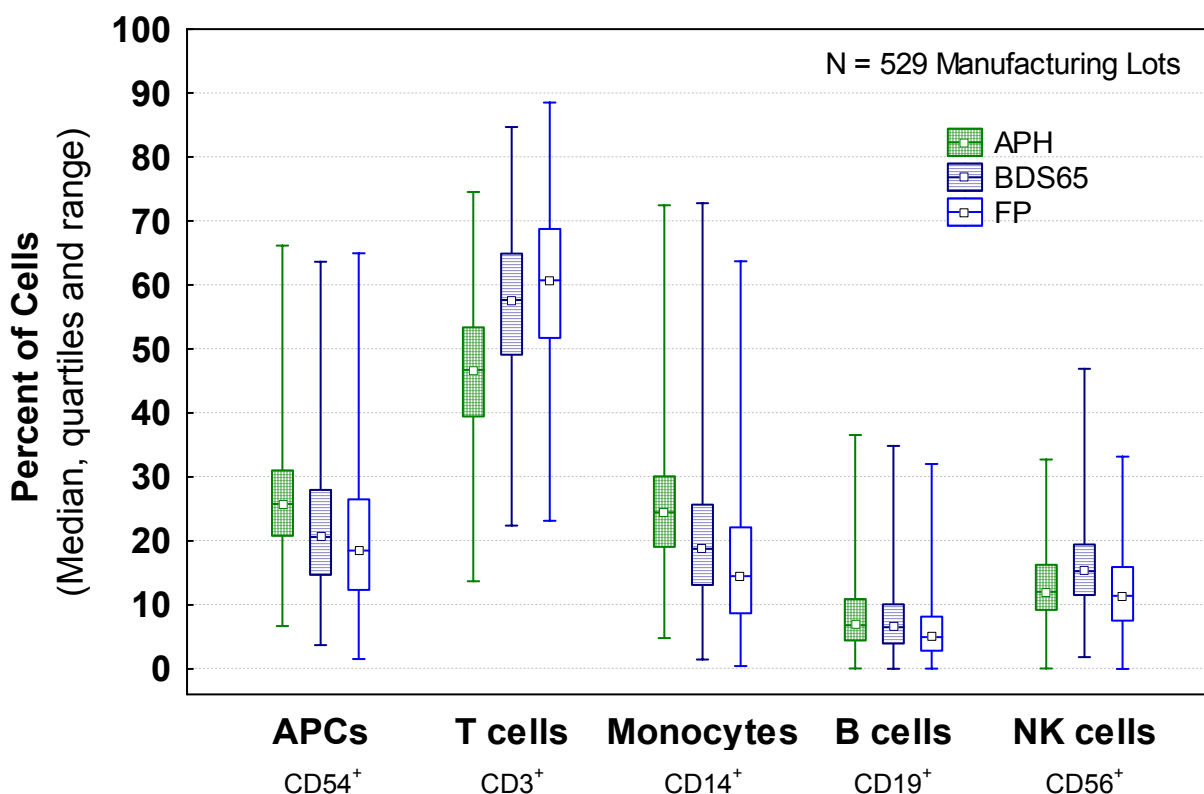
these APCs also express CD14, and thus are included in the monocyte population. The balance of the sipuleucel-T cell population consists of NK cells and B cells.

Figure 20 Sipuleucel-T Final Product Cellular Composition



The composition of the sipuleucel-T cell population correlates closely with the composition of the leukapheresis starting material obtained from the patient. Figure 21 shows the composition 1) in the starting material, 2) just prior to ex vivo culture with recombinant fusion protein (after BDS65 isolation), and 3) in the final product for these lots of sipuleucel-T. The percentages of each cell type remains relatively constant throughout the manufacturing process. While the cell composition is largely determined by the leukapheresis starting material, and remains relatively constant through the process, APC activation (as measured by CD54 expression) changes significantly as a result of incubation with the recombinant fusion protein. As shown in Figure 15, Figure 16, and Figure 19, CD54 expression increases range from 2-fold to over 15-fold after incubation with PA2024.

Figure 21 Sipuleucel-T Cellular Composition Across the Manufacturing Process



Like APCs, the other cell types in the sipuleucel-T product exhibit changes characteristic of activation at Weeks 2 and 4 compared to Week 0. The changes include increases in cytokine

production, expression of activation markers, and development of effector functions ([Appendix 2](#)). In addition, T cell immune responses measured from patients after treatment demonstrate a robust response to the immunizing antigen (Section [6.1.2.5](#) and [Appendix 3](#)). Therefore, other immune cells, in addition to APCs, are engaged after the first infusion of sipuleucel-T.

4.6 Product Characterization Conclusions

Sipuleucel-T characterization studies establish a scientific framework for understanding the sipuleucel-T final product and its effect on immune cells. In vitro models of antigen presentation activity have shown that the product contains activated, antigen-loaded APCs capable of presenting PAP epitopes to T cells.

The activated APCs in sipuleucel-T are all contained within the CD54⁺ cell population, which includes both monocyte-derived APCs and dendritic cells. CD54 expression is the basis for the 2 measures that assess product potency in sipuleucel-T release testing. The first measure is the number of CD54⁺ cells in the final product, which correlates with both PAP antigen presentation activity and costimulatory activity. The second measure is CD54 upregulation, which evaluates the increase in CD54 expression per cell during ex vivo culture. Because CD54 upregulation results from APC activation, this ensures that the APCs administered in sipuleucel-T have been activated. Consistent with the function of CD54 in the immunological synapse, CD54 upregulation correlates with in vitro costimulatory activity. In addition, results from Studies 1 and 2 demonstrate a correlation between CD54 upregulation and clinical outcome as described in Section [6.2.3](#).

The 2 moieties of the PA2024 fusion protein, PAP and GM-CSF, each play a role in generating activated, PAP-presenting APCs. GM-CSF enhances APC viability and activation while the PAP sequences of the recombinant antigen are required to confer specificity to the APC activity, as demonstrated by results from the antigen presentation assay (Section [4.4](#)).

The initial treatment with sipuleucel-T appears to cause changes in the phenotypes and activities of the mononuclear cell populations in the second and third cell products. The activation of patients' T cells, NK cells, and other immune cells during the preparation of the second and third

ex vivo cultures suggests that sipuleucel-T is indeed stimulating an immune response in vivo and that the initial sipuleucel-T treatment also engages elements of the innate immune system ([Appendix 2](#)).

In conclusion, numerous analytical tools have been used to study the biological properties of sipuleucel-T, resulting in a final product that is well-characterized in terms of the following key properties:

- Antigen presenting cell activation as a result of the cell culture step during the manufacturing process;
- PA2024 uptake and presentation of PAP epitopes to T cell hybridomas;
- CD54 expression and upregulation, which correlate with APC function and overall survival ([Section 6.2.3](#)); and
- The cell composition of sipuleucel-T, which correlates closely with the cell composition of the leukapheresis starting material.

5.0 CLINICAL PHARMACOLOGY

Despite the fact that scientists and clinicians have been studying the role of the immune system in cancer biology and therapy for more than 50 years, the precise mechanisms by which the immune system kills cancer cells in vivo remain elusive. Historically, cancer immunotherapies have focused on generating tumor-specific CD8⁺ cytotoxic T lymphocytes (CTLs) as the tumor eliminating effector cells. However, there are multiple, immune-based anti-tumor mechanisms that involve CD4⁺ T cells (both helper cells and rare lytic CD4⁺ cells), NK cells, and B cells. In general, T cells have emerged as the dominant effector cell in targeted active immunotherapy ([Gerloni, 2005](#); [Knutson, 2005](#)). Accordingly, pharmacodynamic immune monitoring of sipuleucel-T has focused on PA2024-specific T cell responses, but studies on the humoral response to PA2024 have also been performed.

5.1 Summary of Preclinical Studies

Preclinical animal studies of sipuleucel-T used a model of rat prostatitis in which rat APCs were pulsed exogenously with a rat PAP rat-GM-CSF fusion protein (rat PAP-GM-CSF) similar to the target antigen in sipuleucel-T ([Laus, 2001](#)). With this model, 2 conditions were identified under which autoimmune prostatitis could be induced: 1) by a primary immunization of rats with APCs pulsed with rat PAP-GM-CSF followed by boosts with this product, and 2) by priming with APCs pulsed with rat PAP-GM-CSF followed by boosts with the recombinant rat-PAP-GM-CSF protein alone. Infusion of rat APCs pulsed exogenously with a control antigen (ovalbumin) and GM-CSF did not induce prostatitis, nor did injection of the fusion protein alone, without first priming the animals with rat PAP-GM-CSF pulsed APCs. These data provided important proof-of-concept regarding the ability of this approach to induce organ-specific, cell-mediated autoimmunity.

5.2 Summary of Phase I and Phase II Studies

The Phase I and Phase II studies of sipuleucel-T, Studies ACT 9610 ([Small, 2000](#)) and ACT 9702 ([Burch, 2000](#); [Burch, 2004](#)), addressed pharmacodynamic issues related to cell dose and frequency that would be appropriate for the Phase III clinical studies.

The immune monitoring data from the Study ACT 9610, in which sipuleucel-T was administered at Weeks 0, 4, and 8, demonstrated that maximal humoral and cellular immune responses against the target PA2024 antigen were achieved at approximately 12 weeks, after the third dose of sipuleucel-T. This study was designed to address the number of cells necessary to elicit a maximal immune response; however, given the relatively small number of men studied, no clear dose relationship was identified. Importantly, minimal toxicity was associated with the administration of sipuleucel-T at all cell doses given and a maximum tolerated dose was not reached. Given the apparent lack of significant toxicity, Dendreon proceeded in later stages of clinical development with the administration of the maximum manufacturable dose (MMD) of cells that could be produced from a single leukapheresis procedure.

Regarding the dose administration schedule, dosing at a 2-week interval (i.e., Weeks 0, 2, and 4) was chosen for the randomized Phase III studies, in contrast to the monthly dosing schedule used previously. This decision was based on data from the second cohort of Study ACT 9702 in which sipuleucel-T was dosed at Weeks 0 and 2, compared to Weeks 0 and 4 in the first cohort. The magnitude of the immune response was not different between these cohorts suggesting that a more compressed dosing schedule was equally immunogenic. From a practical standpoint, it was determined that a bi-weekly interval would be important in men with rapidly progressive disease whose time-to-progression was expected to be 16 weeks (and, indeed, turned out to be even shorter).

Immune response data for the randomized, placebo-controlled Phase III Study 1 are summarized in Section [6.1.2.5](#) and [Appendix 3](#).

6.0 CLINICAL EFFICACY

The proposed basis for licensure from these randomized, double blind, multicenter, placebo-controlled trials is overall survival. In Study 1, the survival results are clinically meaningful, statistically persuasive, and internally consistent in the ITT population. Multiple sensitivity analyses confirm the survival benefit.

Additional supportive evidence of efficacy is provided by a strong trend toward a delay in TTP in Study 1. The survival advantage in Study 1 is further supported by a trend toward prolonged survival in Study 2 and the survival results of the integrated analysis of Studies 1 and 2. The findings are further corroborated by correlations between overall survival and product specific attributes, including potency, collected from each patient.

6.1 Study 1

6.1.1 Design of Study 1

Study 1 was a prospective Phase III, multicenter, double blind, placebo-controlled, randomized trial of immunotherapy with sipuleucel-T for the treatment of men with asymptomatic metastatic AIPC. Major eligibility criteria included the following:

- Metastatic prostate cancer
- No visceral metastases
- Tumor progression despite androgen deprivation (consensus criteria)
- No cancer-related pain
- No systemic steroids or prior immunotherapy
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

Approximately 120 patients were planned for enrollment at 19 investigative centers across the United States. Following a pre-registration and screening process, eligible patients were randomized to either active treatment or control in a 2:1 ratio (active treatment:control;

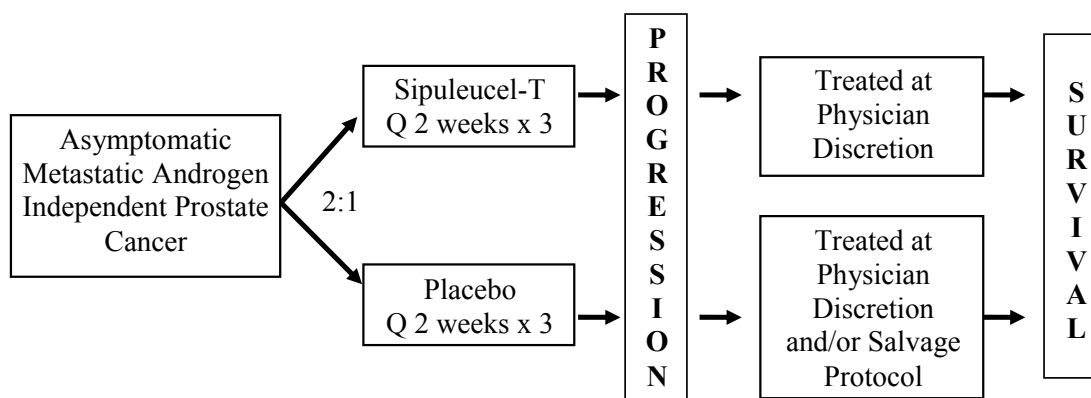
Figure 22). Patients were stratified by bisphosphonate use and study center. Following randomization, patients from both groups underwent a series of 3 standard leukapheresis procedures (in Weeks 0, 2, and 4), and each procedure was followed approximately 2 to 3 days later by infusion of either autologous antigen loaded APCs (sipuleucel-T; active treatment) or autologous quiescent APCs without antigen (placebo; control). The treatment phase of the protocol was complete following the third infusion at Week 4.

To assess the efficacy of treatment, patients were monitored for disease progression by regular radiographic and clinical evaluations. Staging scans were reviewed by an independent radiology facility to confirm objective disease progression. Tumor staging was performed at baseline, Weeks 8, 16, 24, and 32, and every 12 weeks thereafter until disease progression.

Prostate-specific antigen was not used as a measure of progression. Patients were monitored for survival at 2 months following disease progression and every 6 months after randomization until death or for 36 months, whichever occurred first.

At the time that patients were confirmed to have developed disease progression, study treatment could be unblinded, and patients were then treated at the physician's discretion. Patients in the placebo group had the option to enter a Phase II, open label, single-arm salvage trial (Protocol D9903) in which they received a version of sipuleucel-T prepared from the cryopreserved cells remaining after placebo generation. Patients treated with sipuleucel-T were not eligible to participate in the salvage trial.

Figure 22 Treatment Schema



6.1.1.1 Description of Placebo

In order to maintain the blind of the study, all patients, including those assigned to receive placebo control, underwent leukapheresis. For patients randomized to the placebo group, the quiescent APCs were prepared from the leukapheresis and divided into 2 unequal aliquots. One-third of the APCs were stored at 4°C in the absence of antigen, and without activating conditions, to prepare placebo, and two-thirds of the APCs were cryopreserved for later preparation of an investigational product similar to sipuleucel-T (APC8015F) in the event patients entered the Phase II open label salvage protocol (Study D9903). Placebo cells were thus not exposed to the PA2024 antigen and were not held under activating conditions.

6.1.1.2 Description of Salvage Product, APC8015F

For reasons of patient accrual, a salvage protocol was offered to placebo patients following disease progression. Since requesting patients to undergo 3 additional leukaphereses was thought to be too invasive for the salvage study, a portion of cells cryopreserved at the time of placebo generation was used to generate the salvage product, APC8015F. The cryopreserved quiescent autologous PBMCs (including APCs) from 1 leukapheresis product (two-thirds of the PBMCs originally isolated for placebo) were thawed and cultured for approximately 2 days in the presence of PA2024, the recombinant fusion protein.

6.1.1.3 Study Endpoints

The primary measure of efficacy of sipuleucel-T for this BLA is the demonstrated survival benefit, supported by a strong trend toward a delay in TTP. Although survival was not originally defined as a primary efficacy endpoint of Study 1, an analysis of overall survival after 36 months of follow-up in all patients was specified in the protocol and the statistical analysis plan.

Primary Endpoint

The primary endpoint of Study 1 was TTP, defined by any of the following:

- Progressive disease on serial radiographic imaging tests (tumor staging was performed at baseline, Weeks 8, 16, 24, and 32, and every 12 weeks thereafter until disease progression),

- New cancer-related pain associated with a radiographic anatomical correlation, or
- Other clinical events consistent with progression such as spinal cord compression, nerve root compression, or pathologic fracture.

For patients with both independently confirmed radiographic progression and other clinical progression events, the date of independently confirmable radiographic progression was used as the date of disease progression.

Secondary Endpoints

The secondary endpoints were the following:

- Time to disease-related pain (TDRP). (The Study 1 and Study 2 results were to be pooled in order to have sufficient power for this endpoint; Study 1 was also analyzed independently.)
- Response rate and duration of response.
- Time to first evidence of clinical progression.
- Time to treatment failure.
- The incidence of Grade 3 and greater treatment-related adverse events (AEs).

Overall Survival Analysis

The analysis of the 3-year survival data was based on the ITT population of all 127 randomized patients in Study 1. As described in the protocol and statistical analysis plan, every patient was followed until death or the pre-specified cut-off of 36 months following randomization; there were no censored events prior to the 36th month of follow-up.

6.1.1.4 Statistical Methods

The sample size for Study 1 was based on an HR of 1.925 or an increase in TTP, from an estimated 4 months in the placebo arm to 7.7 months in the sipuleucel-T arm, with 80% power, and an overall 2-sided level of significance of 0.05. Efficacy analyses were based on the ITT population, which included all randomized patients. Time-to-event endpoints (e.g., overall survival and TTP) were tested using the log rank test; time-to-event percentiles were based on

the Kaplan-Meier method. Hazard ratios and 95% confidence intervals (Cis) were constructed using Cox regression models for each comparison of interest; unless otherwise specified, the sipuleucel-T arm was used as the denominator to determine the HRs. Cox regression models were also used to perform single or multiple prognostic factor/covariate (either fixed or time-dependent) adjusted analyses. For the prostate cancer specific survival analyses, 1 minus cumulative incidence curves and associated percentiles were provided to account for competing event (other deaths).

For safety data, patients who underwent at least 1 leukapheresis were included in the safety population and Fisher's exact tests were used to evaluate potential trends. P-values from t-tests and Cochran Mantel-Haenszel tests were used to assess trends in demographic and baseline data. Immunology data were analyzed using the Wilcoxon rank sum test.

Two-sided nominal p-values were reported for all statistical tests.

6.1.2 Results of Study 1

6.1.2.1 Demographic and Baseline Characteristics

Table 3 shows the balance of baseline characteristics and laboratory evaluations between treatment arms. The treatment groups were similar with regard to the distribution of age, weight, race, performance status, and prior chemotherapy for prostate cancer. Less than 10% of patients in both treatment arms received prior chemotherapy. The groups were also comparable with regard to a variety of potentially prognostic laboratory values (including baseline PSA, PAP, alkaline phosphatase, hemoglobin, and lactate dehydrogenase [LDH]). The p-values were > 0.05 for all comparisons of the demographic data.

Table 3 Baseline Characteristics and Laboratory Values in Study 1, ITT Population

Characteristic	Sipuleucel-T (n = 82)	Placebo (n = 45)
Median Age, years (range)	73 (47 – 85)	71 (50 – 86)
Median Weight (pounds)	194.1	186.5
ECOG 0 (%)	75.6	82.2
Ethnicity: Caucasian, (%)	89.0	93.3
Median PSA, ng/mL	46.0	47.9
Median PAP, ng/mL	7.0	6.5
Median alk. phos., U/L	102.0	92.0
Median hemoglobin, g/dL	13.0	13.1
Median LDH, U/L	173.5	172.0
Prior Chemotherapy Use (% Yes)	3.7	8.9

The percentage of patients with well or moderately differentiated tumors as assessed by Gleason score (≤ 7) was comparable between the treatment groups ([Table 4](#)). There was a greater percentage of patients in the sipuleucel-T arm with bone-only disease (42.0% in sipuleucel-T arm versus 23.8% in placebo arm) and with > 10 bone metastases (41.5% in sipuleucel-T arm versus 26.7% in placebo arm). The p-values for these differences were > 0.05 .

Table 4 Baseline Disease Parameters in Study 1, ITT Population

Characteristic	Sipuleucel-T (n = 82)	Placebo (n = 45)
Tumor differentiation (%)		
Gleason score ≤ 7	61.0	55.6
Gleason score > 7	39.0	44.4
Disease Location, (%) ^a		
Bone only	42.0	23.8
Soft tissue only	6.2	7.1
Bone and soft tissue	51.9	69.0
Number of Bone Metastases per patient, (%)		
≤ 10	58.5	73.3
> 10	41.5	26.7

^aLocalization of disease could not be determined for 4 patients (1 patient treated with sipuleucel-T; 3 patients treated with placebo) due to lack of baseline scans for soft tissue disease.

Balance between treatment arms for baseline prognostic factors was assessed using an independently validated model (Halabi, 2003). This model was developed and validated on data from a total of 1,101 men with metastatic AIPC enrolled in 6 cooperative group trials. The model provides an estimated survival for a patient using the following baseline prognostic factors: LDH, PSA, alkaline phosphatase, Gleason score, hemoglobin, and the presence of visceral disease. Results of the analysis demonstrate that the treatment arms were well-balanced. The median of the estimated survival times for the patients in the sipuleucel-T and the placebo arms were highly comparable, at 20.1 and 19.9 months, respectively.

6.1.2.2 Primary Endpoint, Time to Disease Progression

The Kaplan-Meier curves for TTP separate at approximately 10 weeks, and remain separated for the duration of follow-up (Figure 23). Patients treated with sipuleucel-T demonstrated a 31% reduction in the risk of TTP relative to those treated with placebo (HR = 1.45 [95% CI: 0.99,

2.11]; $P = 0.052$). The estimated median TTP was 11.7 weeks in the sipuleucel-T group compared with 10.0 weeks in the placebo group. Consistent with the separation of the Kaplan-Meier curves, this difference was greater at the 75th percentile, where the TTP was 25.0 weeks in the sipuleucel-T group compared with 16.3 weeks in the placebo group (Table 5). At 24 weeks, 31.9% of the subjects treated with sipuleucel-T and 13.3% of the subjects treated with placebo were progression-free.

Figure 23 Time to Disease Progression in Study 1 (Kaplan-Meier Method), ITT Population

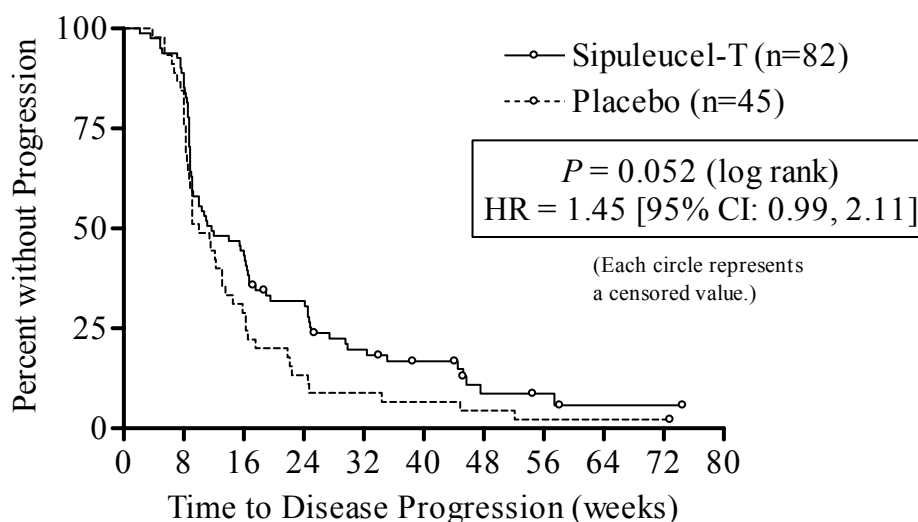


Table 5 Summary Statistics for Overall Time to Disease Progression in Study 1, ITT Population

Treatment	Number of Patients	Percent with Progression (weeks)			Progression-Free Rates		
		25%	50%	75%	12 weeks	24 weeks	36 weeks
Sipuleucel-T	82	8.7	11.7	25.0	48.1	31.9	16.8
Placebo	45	8.3	10.0	16.3	44.4	13.3	6.7

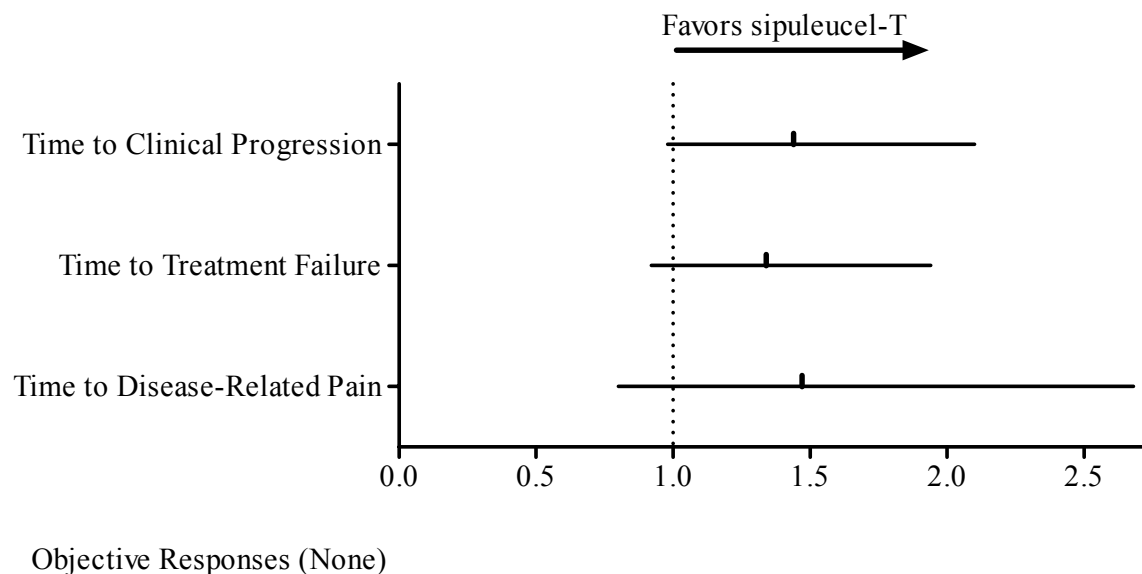
It should be noted that the initial p-value reported for TTP was 0.085. After unblinding, further analyses of TTP were performed to better understand the efficacy of sipuleucel-T and several errors were found that, once corrected, resulted in an improved p-value; the HR remained the same. These errors included improper censoring applied to patients with post randomization protocol deviations, typographical errors, and use of a clinical progression date rather than the objective disease progression date specified in the statistical analysis plan. After correcting for these errors, the log rank p-value for the primary endpoint was 0.052 and the HR was 1.45.

As noted in Section 2.2.2, TTP has proven to be a challenging endpoint in advanced prostate cancer given the reliance on bone scan imaging and the inconsistent correlation with overall survival. In addition, at the time the study was designed, the median TTP in the placebo arm was estimated to be 16 weeks, based on the assumption that patients with asymptomatic disease would progress more slowly than symptomatic patients, thus, allowing more time for immunotherapy to take effect. However, in Study 1, it was learned that asymptomatic patients progress at rates that are comparable to those with symptomatic disease, as has been subsequently confirmed by data from the zoledronic acid and atrasentan studies (Ibrahim, 2005; Saad, 2002; Tang, 2005). The median TTP in Study 1 was 10 to 12 weeks, such that approximately 30% of the patients had already progressed by the time of the first scan at 8 weeks. Furthermore, because of the time required to mount an effective immune response, many patients likely progressed before an optimal immune response was achieved.

6.1.2.3 Secondary Endpoints

The results of the secondary endpoints of time to clinical progression, time to treatment failure, and TDRP showed a trend in favor of patients treated with sipuleucel-T versus patients treated with placebo (all p-values > 0.05). Specifically the HRs were all in the same direction in favor of the sipuleucel-T arm (Figure 24). No patients experienced a tumor response based on review by the central radiology facility.

Figure 24 Summary of Secondary Endpoints, Study 1

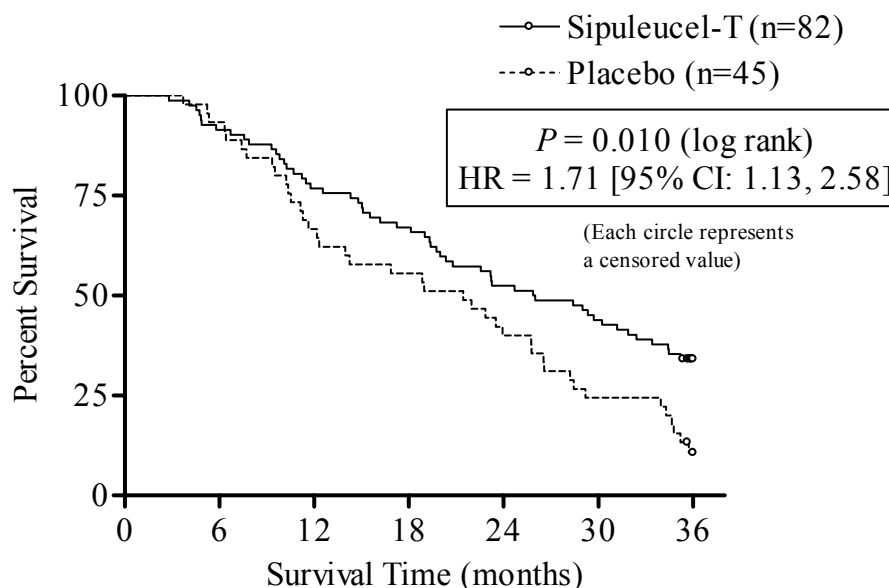


6.1.2.4 Overall Survival

Intent-to-Treat Analysis

In the analysis of the 36-month survival data of all 127 patients in the ITT population, Study 1 demonstrated an improvement in overall survival for patients treated with sipuleucel-T (HR = 1.71 [95% CI: 1.13, 2.58]; $P = 0.010$; [Figure 25](#)). This represents a 41% reduction in the risk of death for patients randomized to sipuleucel-T.

Figure 25 Overall Survival in Study 1 (Kaplan-Meier Method), ITT Population



The median survival time for patients treated with sipuleucel-T was 4.5 months longer than that for patients treated with placebo (median survival times of 25.9 months [95% CI: 20.0, 32.4] and 21.4 months [95% CI: 12.3, 25.8], respectively [Table 6]). This 4.5 month difference in median survival between treatment arms contrasts with the comparable estimated survival times for the treatment arms using the Halabi model (20.1 and 19.9 months for the sipuleucel-T and placebo arms, respectively; Section 6.1.2.1) and suggests that the observed difference in survival is due to the treatment effect. At the 36-month follow-up visit, 34.1% (n=28) of the patients randomized to sipuleucel-T were alive compared to 10.7% (n=5) of the patients randomized to placebo. All patients were followed until death or for 36 months following randomization, whichever occurred first; no patients were lost to follow-up (censored prior to the 36-month follow-up visit) for the survival analysis.

Table 6 Summary Statistics for Overall Survival in Study 1, ITT Population

Treatment	Number of Patients	Deaths Over 36-Month Follow-Up	Death Percentiles, months			Survival Rates		
			25%	50%	75%	12 Months	24 Months	36 Months
Sipuleucel-T	82	54 (66%)	14.3	25.9	≥ 35.2	76.8%	52.4%	34.1%
Placebo	45	40 (89%)	10.5	21.4	29.2	66.7%	40.0%	10.7%

Robustness of the Survival Benefit

In order to determine if there were any undue influences on the overall survival results of Study 1 other than treatment effect, sensitivity analyses were performed to test the robustness of the survival results. These analyses included the following:

- Consistency of the treatment effect in study sub-populations
- Adjustment for potential imbalances in baseline prognostic factors
- Assessment of chemotherapy use and timing following study treatment
- Prostate cancer-specific survival

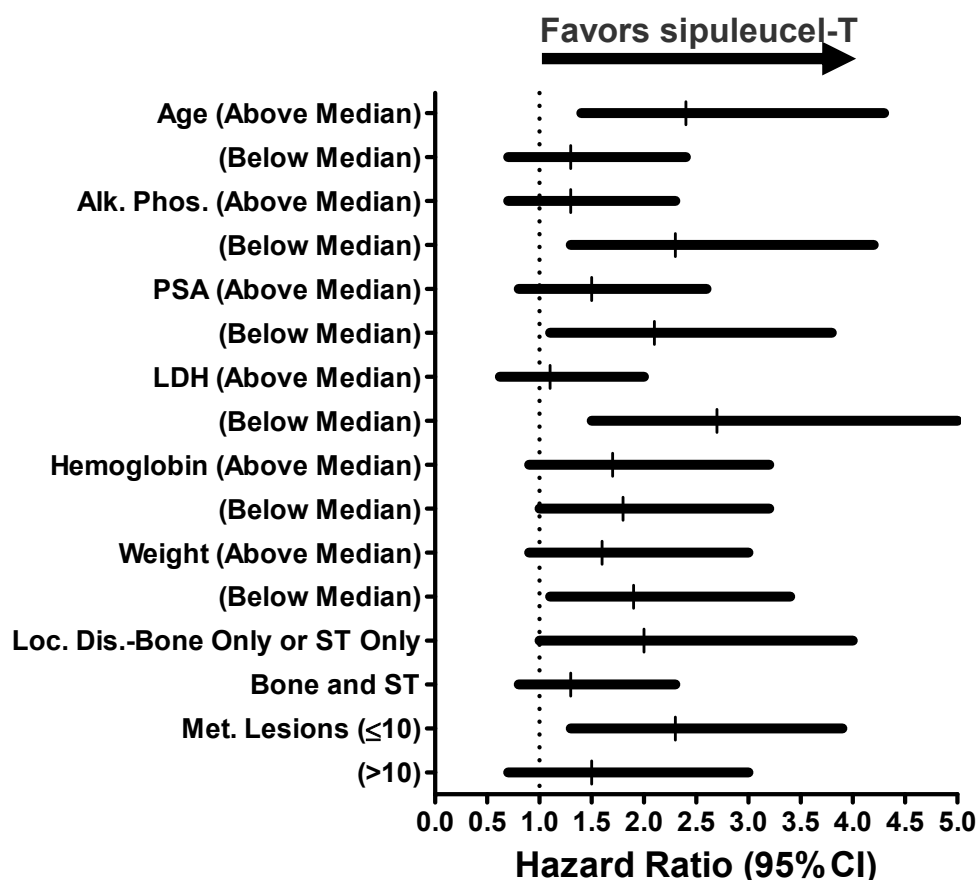
Consistency of the Treatment Effect in Study Sub-Populations

The treatment effect of sipuleucel-T relative to placebo was assessed in sub-populations of patients based on 21 potential or known prognostic factors. For continuous variables, the treatment effect was assessed for patients with values above versus below the median value.

[Figure 26](#) presents the treatment effect for sub-populations for the 8 factors (age, alkaline phosphatase, hemoglobin, LDH, localization of disease, bone lesion count, PSA, and weight), which were identified as predictors of survival individually at the $P \leq 0.05$ level, independent of the treatment effect. These 8 factors are well described in the literature ([Appendix 4](#)).

Additional sub-populations for other prognostic factors are provided in [Appendix 5](#). There was consistent evidence of a positive treatment effect ($HR > 1.00$) in these sub-populations based on the 21 prognostic factors.

Figure 26 Consistent Sipuleucel-T Treatment Effect in Study Sub-populations Based on the 8 Baseline Prognostic Variables found to be Predictive for Overall Survival at the $P \leq 0.05$ Level, Study 1



Adjustment for Potential Imbalances in Baseline Prognostic Factors and Improvement in the Precision of the Estimated Treatment Effect

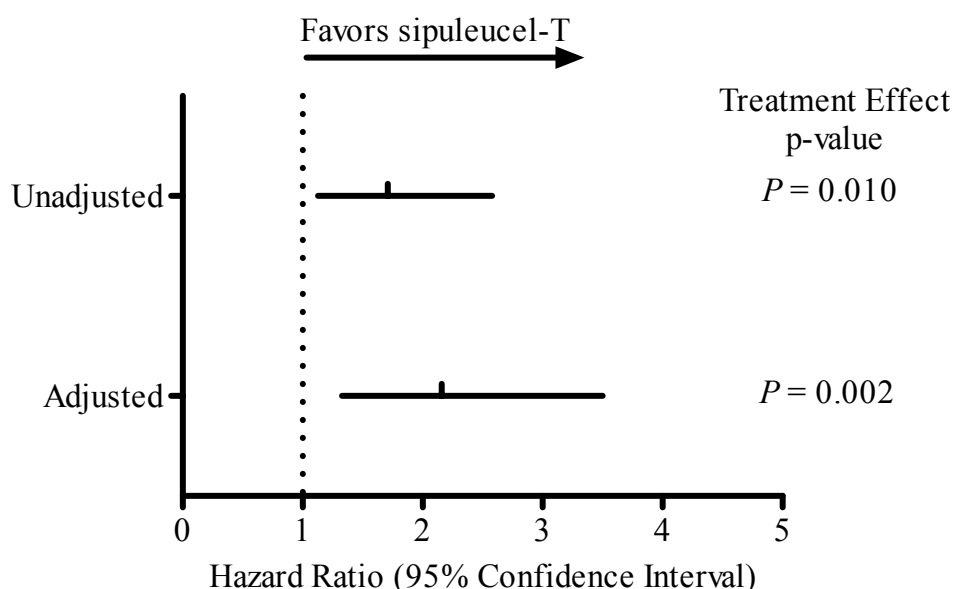
To adjust for potential imbalances in baseline prognostic factors and improve the precision of the estimated treatment effect, the 21 prognostic factors described above were individually evaluated in separate Cox models ([Appendix 6](#)). The p-value was ≤ 0.05 for the treatment effect associated with sipuleucel-T in each of the 21 Cox models using a single prognostic factor as a covariate.

The treatment group statistics show that the treatment effect remained strong ($HR \geq 1.60$ and $p\text{-value} \leq 0.05$) in all analyses, providing evidence that the treatment effect observed in this study is not attributable to the individual effect of the prognostic factors tested or to potential imbalances between treatment groups in these factors at baseline.

In order to build a model with prognostic factors that was predictive of survival jointly, the 8 prognostic factors identified as predictive for overall survival in the univariate analyses were considered as candidates and included in a Cox multiple regression model. Because some of these factors were correlated, a stepwise selection method was used to identify independent prognostic factors.

The results of this analysis reduced the number of prognostic factors remaining in the model to 5. The 5 baseline prognostic factors that remained in the final model were LDH (natural log [ln]), PSA (ln), localization of disease, bone lesion count, and body weight in pounds. It should be noted that the treatment effect continued to be significant at every step of the selection procedure and was a significant predictor of survival in the final model. Following Cox model adjustment for these 5 prognostic factors, the treatment effect remained strong (HR = 2.16 [95% CI: 1.33, 3.50]; $P = 0.002$; Figure 27).

Figure 27 Summary of Survival Benefit Confirmed by Cox Model Adjustment for Multiple Baseline Prognostic Factors, Study 1



Assessment of Chemotherapy Use and Timing Following Study Treatment

In order to assess whether the use of chemotherapy, in particular the use of docetaxel, influenced the survival results, the 2 treatment groups were compared with respect to the administration of chemotherapy use following protocol treatment. This analysis revealed that the administration of chemotherapies between treatment groups was comparable; 54.4% of patients who received sipuleucel-T and 62.8% of patients who received placebo were treated with any chemotherapy following disease progression (Table 7). More specifically, 43.6% of patients who received sipuleucel-T and 53.7% of patients who received placebo were subsequently treated with a taxane-based chemotherapy; 37.2% of patients treated with sipuleucel-T and 48.8% of placebo-treated patients received docetaxel. Differences in chemotherapy use (both taxane and non-taxane based) could not be demonstrated.

Table 7 Chemotherapy Use Following Therapy in Study 1

Chemotherapy	Sipuleucel-T (n = 78) n (%)	Placebo (n = 41) n (%)	p-value (Fisher's Exact)
Docetaxel	29 (37.2%)	20 (48.8%)	0.244
Chemotherapy other than taxanes	34 (43.6%)	13 (31.7%)	0.240
Taxane-based chemotherapy	34 (43.6%)	22 (53.7%)	0.337
Any chemotherapy ^a	43 (54.4%)	27 (62.8%)	0.445

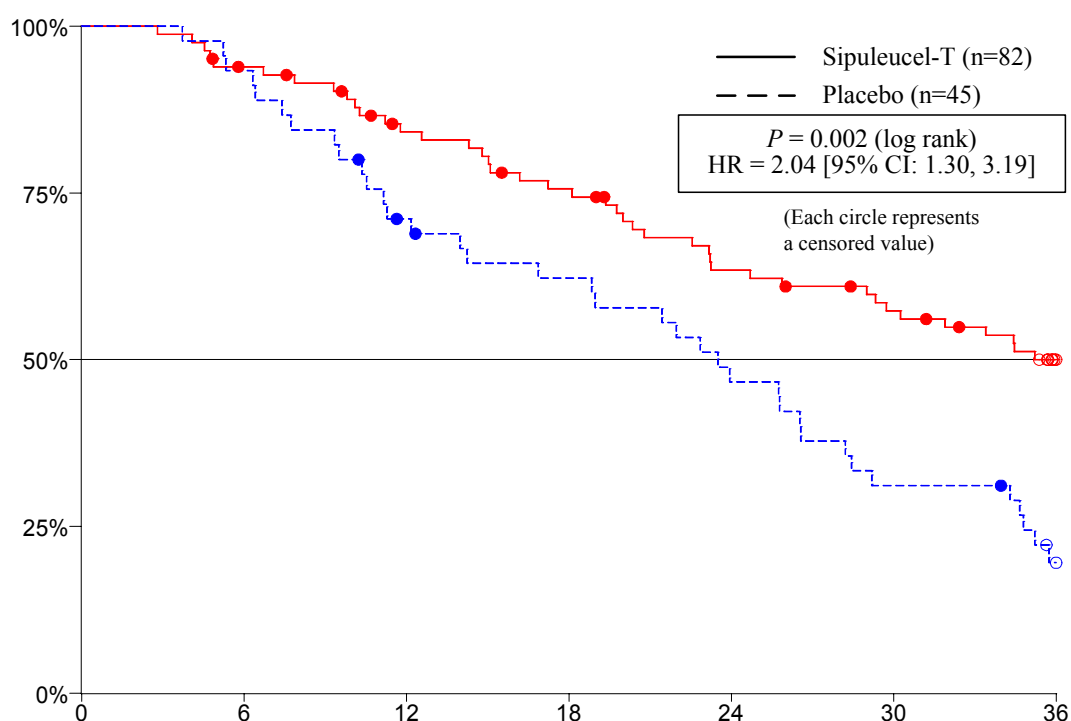
^aFor "Any chemotherapy" there were 79 patients in the sipuleucel-T arm and 43 patients in the placebo arm.

Further analyses were performed to determine whether the time to initiation of chemotherapy or docetaxel influenced the observed survival outcome. There was no evidence to suggest a delay in the time to initiation of any chemotherapy or specifically docetaxel chemotherapy in the placebo arm relative to the sipuleucel-T arm. Finally, the treatment effect for sipuleucel-T persisted after adjustment for time to any chemotherapy (HR = 1.60 [95% CI: 1.04, 2.45]; $P = 0.031$) or time to docetaxel chemotherapy (HR = 1.54 [95% CI: 1.00, 2.38]; $P = 0.052$) in a Cox regression model.

Prostate Cancer-Specific Survival

In order to understand the potential influence of non-prostate cancer deaths, prostate cancer-specific survival was determined. Based on a review of Investigator determination of the cause of death, and death certificates when available, 17 of the 94 deaths on-study were not attributed to prostate cancer or probable prostate cancer. To determine prostate cancer-specific survival, the deaths not attributed to prostate cancer were censored at the time of the competing death. Compared to the overall survival analysis, the treatment effect remained strong (HR = 2.04 [95% CI: 1.30, 3.19]; $P = 0.002$; Figure 28).

Figure 28 Prostate Cancer-specific Survival in Study 1 (Cumulative Incidence Method), ITT Population

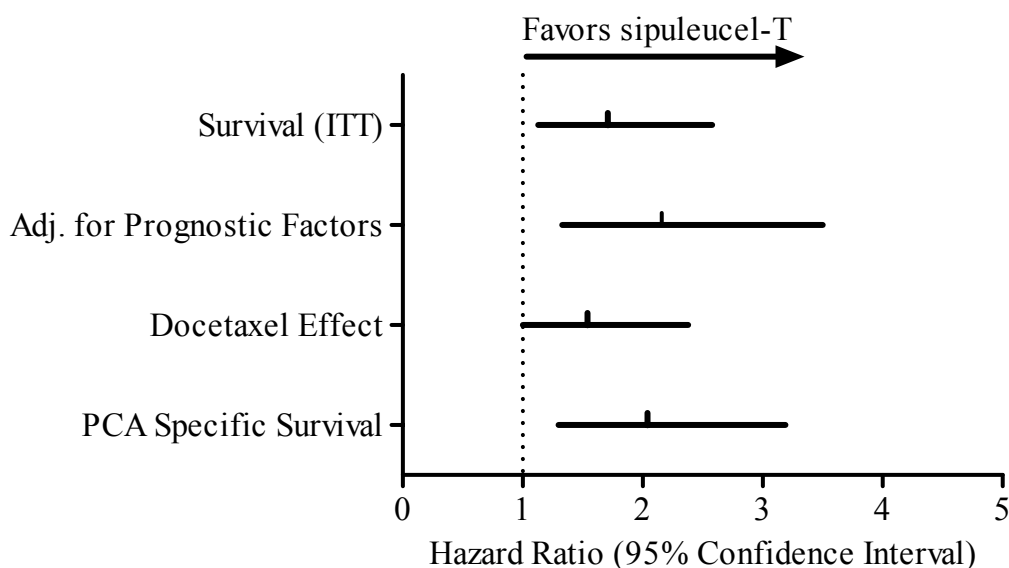


Summary of Sensitivity Analyses

The results of these sensitivity analyses support the survival benefit conferred by sipuleucel-T, and demonstrate the robustness of the survival advantage. The treatment effect was consistent among multiple sub-populations based on 21 known or potential prognostic factors. In addition, the treatment effect remained consistently strong after performing adjustments for potential

imbalances in baseline prognostic factors individually or jointly, chemotherapy use following study treatment, and prostate cancer-specific survival (Figure 29).

Figure 29 Summary of Sensitivity Analyses, Study 1



6.1.2.5 Immune Response

Assessments for cellular and humoral immune responses were performed as exploratory analyses in a subset of patients (n = 49) and are presented in [Appendix 3](#). While immune response to PA2024 has proven a robust, reliable, and useful tool for the clinical development of sipuleucel-T, demonstration of an immune response to PAP has proven more challenging ([Table 28](#) and [Table 29](#) in [Appendix 3](#)). It is unclear whether this is due to a dearth of PAP-specific T cells, suboptimal timing or location of sampling, or issues with the assay methods. These are technical concerns that Dendreon, and the field of immunotherapy in general, will continue to investigate.

6.2 Supportive Evidence

The survival advantage observed in Study 1 is supported by a trend toward prolonged survival in the supportive Study 2 and the survival results of the integrated analysis of Studies 1 and 2.

6.2.1 Study 2

6.2.1.1 Design of Study 2

Study 2 was originally designed as an identical companion study to Study 1 (as noted above) and was designed to include 120 patients randomized 2:1 to sipuleucel-T or placebo. Patients were stratified by bisphosphonate use and study center. Enrollment in Study 2 was stopped at 98 patients (short of the planned 120) based on the TTP findings from Study 1 suggesting that Study 2 was unlikely to meet the TTP endpoint. Although enrollment was stopped early, the study remained blinded and all patients were followed for efficacy and safety, including the 36 month follow-up for survival.

Study Endpoints

After analysis of Study 1, following discussions with the Agency, and prior to unblinding, the statistical analysis plan for Study 2 was revised (dated 29 NOV 2004) to reflect the endpoints described below.

Primary Endpoint

The primary endpoint of Study 2 was TTP, as defined in Section [6.1.1.3](#).

Secondary Endpoints

The secondary endpoints were revised to include the following:

- Overall survival
- Time to objective disease progression confirmed by imaging studies

The tertiary endpoints included response rate, duration of response, and TDRP.

As noted in Section [3.0](#), enrollment in Study 2 was discontinued early. The analysis of the 3-year survival data was based on the ITT population of all 98 randomized patients in Study 2. Per the statistical analysis plan, survival was evaluated after the 96th patient had been followed

for 3 years following randomization, at which point 2 additional patients were censored for survival and included in the 36-month analysis at 25.6 and 26.7 months.

Statistical Methods

Statistical methods for Study 2 were identical to those for Study 1 as described in Section 6.1.1.4.

6.2.1.2 Results of Study 2

Demographic and Baseline Characteristics

Table 8 shows the balance of baseline characteristics and laboratory evaluations between treatment arms. The treatment groups were similar with regard to the distribution of age, weight, race, performance status, and prior chemotherapy for prostate cancer. The groups were also comparable with regard to a variety of potentially prognostic laboratory values (including baseline PSA, PAP, alkaline phosphatase, hemoglobin, and LDH). The p-value was > 0.05 for all comparisons of the demographic data.

Table 8 Baseline Characteristics and Laboratory Values in Study 2, ITT Population

Characteristic	Sipuleucel-T (n = 65)	Placebo (n = 33)
Median Age, years (range)	70 (51 – 84)	71 (57 – 87)
Median Weight (pounds)	191.3	184.0
ECOG 0 (%)	78.5	69.7
Ethnicity: Caucasian, (%)	90.8	93.9
Median PSA, ng/mL	61.3	44.0
Median PAP, ng/mL	4.5	5.1
Median alk. phos., U/L	140.0	105.0
Median hemoglobin, g/dL	12.8	12.6
Median LDH, U/L	187.0	179.0
Prior Chemotherapy Use (% Yes)	11.1	9.1

There was a greater percentage of patients in the sipuleucel-T arm who entered the study with well or moderately differentiated tumors as assessed by Gleason score (68.7% in sipuleucel-T

arm versus 51.5% in placebo arm), with bone only disease (47.7% in sipuleucel-T arm versus 30.3% in placebo arm) and with more than 10 metastatic lesions (50.8% in sipuleucel-T arm versus 37.5% in placebo arm; Table 9). The p-values for these differences were > 0.05.

Table 9 Baseline Disease Parameters in Study 2

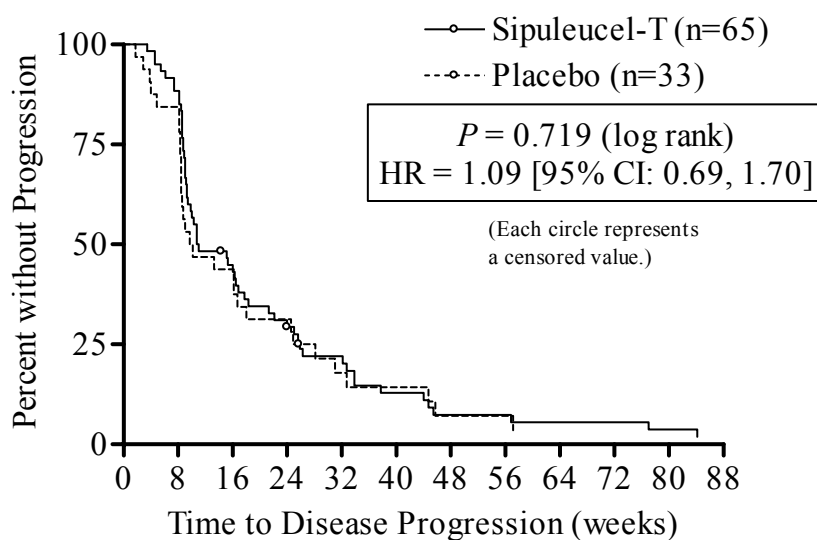
Characteristic	Sipuleucel-T (n = 65)	Placebo (n = 33)
Tumor differentiation (%)		
Gleason score ≤ 7	68.7	51.5
Gleason score > 7	31.3	48.5
Disease Location, (%)		
Bone only	47.7	30.3
Soft tissue only	10.8	21.2
Bone and soft tissue	41.5	48.5
Number of Bone Metastases per patient, (%) ^a		
≤ 10	49.2	62.5
> 10	50.8	37.5

^aFive patients did not have readings of baseline bone scans by the central radiology facility.

Primary Endpoint, Time to Disease Progression

When the Kaplan-Meier curves for overall TTP were compared, there was no significant difference between the 2 arms (HR = 1.09 [95% CI: 0.69, 1.70]; *P* = 0.719; [Figure 30](#)).

Figure 30 Overall Time to Disease Progression in Study 2 (Kaplan-Meier Method), ITT Population



Other endpoints

During the trial, available imaging studies were evaluated for all patients by a central, independent radiology facility. An analysis was conducted on time from randomization to objective disease progression confirmed by imaging studies. (This analysis differed from the primary efficacy evaluation in that patients who progressed by clinical, non-radiographic criteria in the primary efficacy evaluation were censored at the last imaging exam date in this analysis.) This analysis demonstrated an HR of 1.17 ([95% CI: 0.71, 1.92]; $P = 0.538$).

One patient treated with sipuleucel-T experienced a tumor response based on review by the central radiology facility; the patient experienced a partial response at Week 16 that lasted through Week 32.

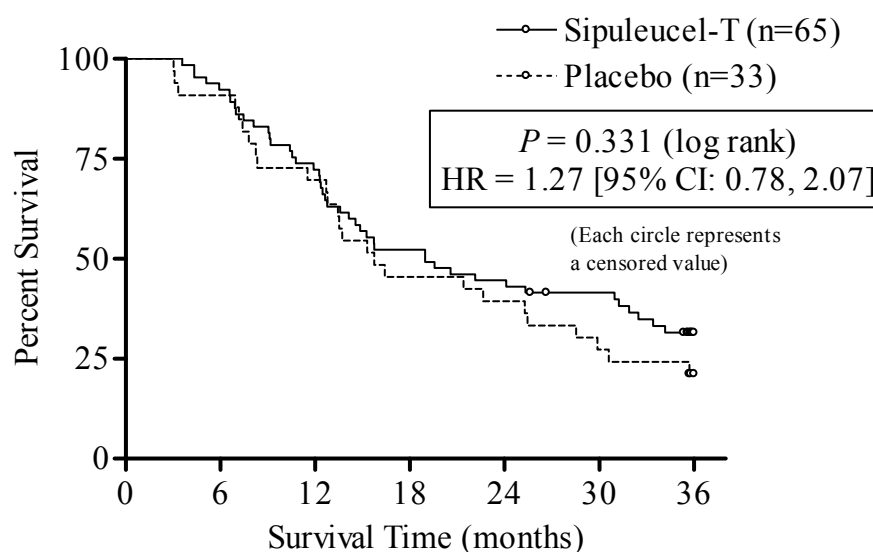
For the TDRP endpoint in Study 2, the HR was 0.71 ([95% CI: 0.33, 1.52]; $P = 0.376$). In the integrated analysis of TDRP in Studies 1 and 2, an analysis specified in the protocols and statistical analysis plans, the HR was 1.47 ([95% CI: 0.80, 2.68]; $P = 0.210$).

Overall Survival

Primary Analysis

The analysis of the 36-month survival data of all 98 patients in the ITT population showed a trend in the same direction as Study 1. Patients treated with sipuleucel-T had a 21% reduction in the risk of death (HR = 1.27 [95% CI: 0.78, 2.07]; $P = 0.331$; Figure 31).

Figure 31 Overall Survival in Study 2 (Kaplan-Meier Method), ITT Population



The median survival time for patients treated with sipuleucel-T was 3.3 months longer than that for patients treated with placebo (median survival times of 19.0 months and 15.7 months, respectively; [Table 10](#)). At the 36-month follow-up visit, the proportion of patients in the sipuleucel-T group who were alive was higher than that of the placebo group (31.6% versus 21.2%, respectively). No patient was lost to follow-up for the survival analysis; with the exception of 2 patients censored at 25.6 and 26.7 months, all patients were followed until 36 months for survival.

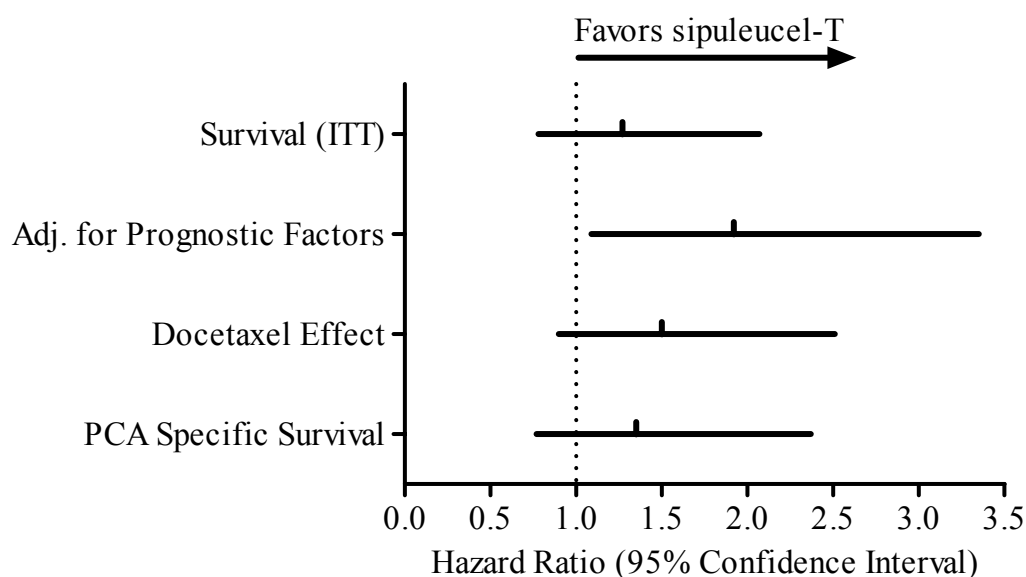
Table 10 Overall Survival Summary Statistics in Study 2, ITT Population

Treatment	Number of Patients	Deaths Over 36-Month Follow-Up	Death Percentiles, months			Survival Rates		
			25%	50%	75%	12 Months	24 Months	36 Months
Sipuleucel-T	65	44 (67.7%)	10.8	19.0	≥31.9	72.3%	44.6%	31.6%
Placebo	33	26 (78.8%)	8.3	15.7	30.6	69.7%	39.4%	21.2%

Survival Sensitivity Analyses

As in Study 1, sensitivity analyses were performed on the Study 2 dataset (Figure 32). The treatment effect was adjusted for potential imbalances in baseline prognostic factors by applying the final model that was developed for Study 1 to the data from Study 2. After adjusting for the 5 factors in the final model, the HR for the treatment effect increased from 1.27 to 1.92 ([95% CI: 1.09, 3.35]; $P = 0.023$). The treatment effect also remained after adjustment for docetaxel use following investigational therapy (HR = 1.50 [95% CI: 0.90, 2.51]; $P = 0.121$). Prostate cancer-specific survival revealed an HR of 1.35 ([95% CI: 0.08, 2.37]; $P = 0.287$).

Figure 32 Summary of Sensitivity Analyses, Study 2



Relevance of the Overall Survival Results

Study 2 demonstrates a trend toward prolongation of survival for patients treated with sipuleucel-T relative to placebo (HR = 1.27 [95% CI: 0.78, 2.07]; $P = 0.331$). The observed HR in Study 2 was lower than that in Study 1 (HR = 1.71). However, the 95% CIs for the unadjusted HR estimates for each study overlap, and the unadjusted HR estimates for each study lie within each other's CIs. In addition, the treatment effect between Studies 1 and 2 was not different ($P = 0.413$). Enrollment in Study 2 was discontinued early, and therefore provides a less precise estimate of the treatment effect than Study 1.

6.2.2 Integrated Results of Studies 1 and 2

The rationale for integrating the efficacy data for Study 1 and Study 2 are based on the following:

- The trial design was identical for both studies;
- The eligibility criteria were identical for both studies;
- The studies were conducted contemporaneously;
- Twelve of a total of 34 clinical sites were the same for both studies;
- The estimated treatment effect was in the same direction for both studies, indicating no qualitative treatment by study interaction.
- The p-value associated with the treatment by study interaction equaled 0.413, indicating no quantitative treatment by study interaction.

A summary of the integrated demographic and baseline characteristics for Studies 1 and 2 is located in [Appendix 7](#).

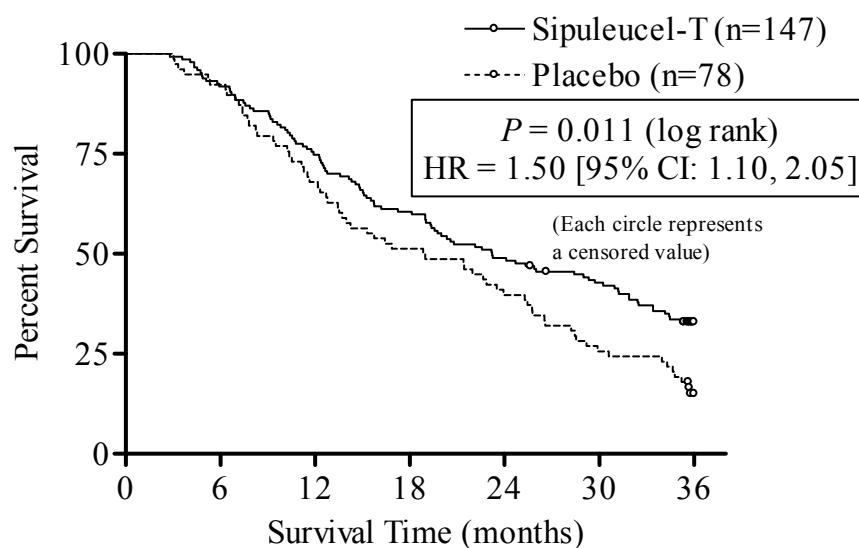
6.2.2.1 Overall Survival

Primary Analysis

A total of 223 or 225 patients from Studies 1 and 2 were followed until death or a cut-off of 36 months after randomization; 2 additional patients (in Study 2) were followed for 25.6 months and 26.7 months at the time of data cut-off. Patients randomized to treatment with sipuleucel-T

had a 33% reduction in the risk of death relative to patients on the placebo arm (stratified by study; HR = 1.50 [95% CI: 1.10, 2.05]; $P = 0.011$; Figure 33).

Figure 33 Integrated Overall Survival (Kaplan-Meier Method) in Studies 1 and 2, ITT Population



The median survival time for patients treated with sipuleucel-T was 4.3 months longer than that for patients treated with placebo (median survival times of 23.2 months and 18.9 months, respectively; [Table 11](#)). At the end of the studies (up to a pre-specified follow-up of 36 months following randomization), the estimated survival rate in the sipuleucel-T group was approximately 2-fold higher than that in the placebo group (32.9% versus 15.1%, respectively).

Table 11 Integrated Summary Statistics for Overall Survival in Studies 1 and 2, ITT Population

Treatment	Number of Patients	Deaths Over 36-Month Follow-Up	Death Percentiles, months			Survival Rates		
			25%	50%	75%	12 Months	24 Months	36 Months
Sipuleucel-T	147	98 (67%)	11.9	23.2	NE	74.8%	49.0%	32.9%
Placebo	78	66 (85%)	10.4	18.9	30.6	67.9%	37.9%	15.1%

NE = Not estimable.

Survival Sensitivity Analyses

Sensitivity analyses similar to those performed for Studies 1 and 2 were performed on the integrated Study 1 and 2 survival results. The treatment effect was consistent among study sub-populations defined by 21 known or potential baseline prognostic factors. The final model that was developed for Study 1 was applied to the integrated data. After adjusting for the 5 factors in the final model, the treatment effect remained strong (HR = 1.86 [95% CI: 1.31, 2.63]; $P < 0.001$). The treatment effect also remained after adjustment for docetaxel use following investigational therapy (HR = 1.50 [95% CI: 1.07, 2.08]; $P = 0.017$). Prostate cancer-specific survival revealed an HR of 1.72 ([95% CI: 1.21, 2.44]; $P = 0.002$).

6.2.3 CD54 Upregulation Correlation with Overall Survival

Survival data for patients treated with sipuleucel-T in Studies 1 and 2 were assessed in the context of the key product release specification parameters, specifically, the TNC count, CD54⁺ cell count, and CD54 upregulation ratio. As discussed in Section 4.0, CD54⁺ cell count and CD54 upregulation ratio were chosen as biologically relevant potency parameters because of the ubiquitous expression of CD54 on APCs, the role of CD54 in the immunologic synapse between APCs and T cells, and the level of increased CD54 expression as an indicator of APC activation. Cumulative CD54⁺ cell counts, total nucleated cell (TNC) counts, and CD54 upregulation ratio were calculated as the sum of Week 0, Week 2, and Week 4 final product values for each parameter for each patient in the integrated Study 1 and Study 2 dataset. The median (range) cumulative TNC and CD54⁺ counts infused per patient, as well as the median cumulative CD54 upregulation ratio per patient is summarized in Table 12.

Table 12 Median Cumulative Cell Doses administered in Studies 1 and 2

	APC8015 (n = 146) Median (range)	APC-Placebo (n = 76) Median (range)
TNC	10.0 x 10 ⁹ (0.8 x 10 ⁹ to 36.0 x 10 ⁹)	3.2 x 10 ⁹ (0.8 x 10 ⁹ to 8.6 x 10 ⁹)
CD54 ⁺	2.3 x 10 ⁹ (0.3 x 10 ⁹ to 8.6 x 10 ⁹)	0.9 x 10 ⁹ (0.03 x 10 ⁹ to 7.0 x 10 ⁹)
CD54 Upregulation Ratio	22.3 (2.9 to 46.6)	2.8 (1.2 to 4.1)

Each cumulative parameter was used as a continuous variable in a Cox model to evaluate the correlation between the parameter and overall survival for those patients who received sipuleucel-T. These analyses demonstrated a strong correlation between overall survival and both TNC ($P = 0.018$) and CD54 upregulation ratio ($P = 0.009$; Table 13), which, for CD54 upregulation, persisted after adjustment for baseline prognostic factors (weight, PSA, LDH, number of bone lesions, and localization of disease; $P = 0.022$). A correlation was not observed between overall survival and cumulative total CD54 cell count.

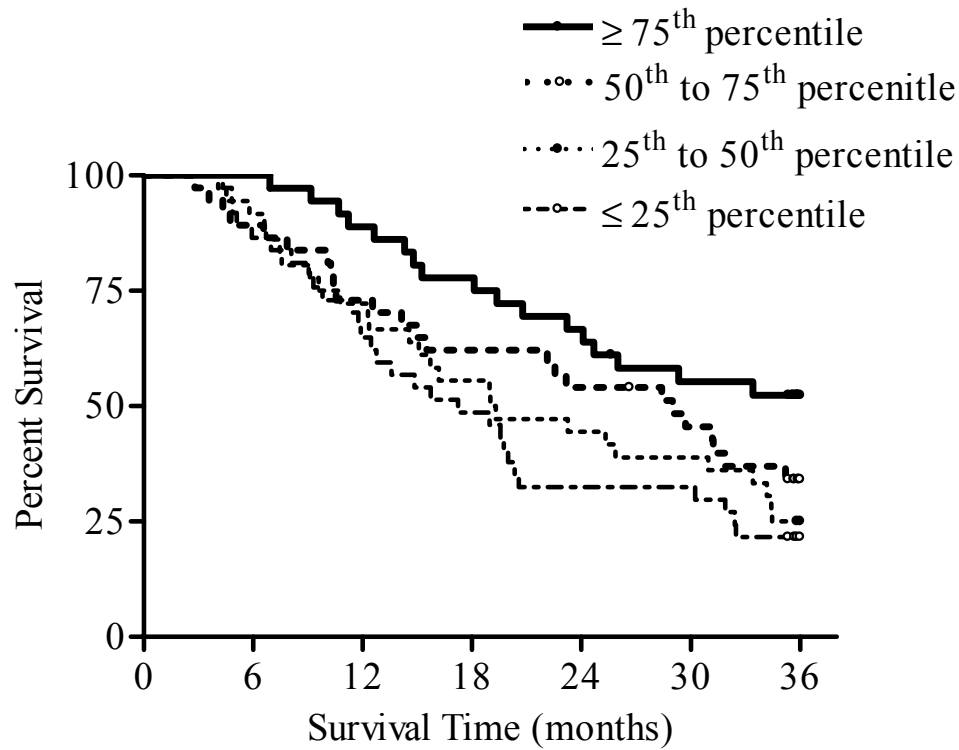
Table 13 Correlation between Cumulative Product Release Parameters and Overall Survival in Patients treated with Sipuleucel-T, Integrated Studies 1 and 2

	Unadjusted (N = 145) p-value	Adjusted (N = 133) p-value
Parameter (basis for HR)		
TNC count (per 1.0 x 10 ⁹)	0.018	0.138
CD54 ⁺ count (per 1.0 x 10 ⁹)	0.354	0.694
CD54 upregulation ratio (per unit)	0.009	0.022

Abbreviations: HR = hazard ratio; TNC = total nucleated cells

The correlation between overall survival and cumulative CD54 upregulation is demonstrated graphically in [Figure 34](#), which show the survival of patients by cumulative CD54 upregulation in quartiles. These results strongly suggest that sipuleucel-T is engaging the immune system and that potency, a key product quality attribute, correlates with clinical outcome.

Figure 34 Sipuleucel-T Survival by Cumulative CD54 Upregulation in Quartiles, Integrated Studies 1 and 2



6.3 Efficacy Conclusions

The evidence for the clinical efficacy of sipuleucel-T is based upon the results of Study 1, a randomized, multicenter, double blind, placebo-controlled trial. The survival results in Study 1, are both clinically meaningful and statistically compelling. These results are supported by the strong trend toward a delay in TTP in Study 1. The overall survival results from Study 2, and the integrated results from Studies 1 and 2, provide additional support.

In Study 1, patients treated with sipuleucel-T demonstrated a 41% reduction in the risk of death compared to patients treated with placebo (HR = 1.71 [95% CI: 1.13, 2.58]; $P = 0.010$). The median survival times were 25.9 months for patients treated with sipuleucel-T and 21.4 months for patients treated with placebo. These survival results were robust, as confirmed by multiple sensitivity analyses, including assessment of the treatment effect in study sub-populations, adjustment for potential imbalances in baseline prognostic factors, adjustment for chemotherapy use following study treatment, and the determination of prostate cancer specific survival. The trend to prolongation of TTP (HR = 1.45 [95% CI: 0.99, 2.11]; $P = 0.052$) provides support for the observed survival benefit in Study 1.

Further supportive evidence of a survival benefit is provided in the smaller companion study, Study 2. While the p-value was 0.331, a benefit from sipuleucel-T is suggested by the HR of 1.27 (95% CI: 0.78, 2.07), indicating a 21% reduction in the risk of death, and the 3.3 month increase in median survival time for patients treated with sipuleucel-T versus placebo (median survival times of 19.0 months and 15.7 months, respectively). The overall survival results of the integrated analysis of Studies 1 and 2 (HR = 1.50 [95% CI: 1.11, 2.05]; $P = 0.011$), provide an additional measure of the treatment effect of sipuleucel-T in men with asymptomatic metastatic AIPC. Finally, the efficacy of sipuleucel-T is supported by the correlation between the product potency parameter, cumulative CD54 upregulation, and overall survival.

In summary, there are multiple lines of evidence supporting the clinical efficacy of sipuleucel-T. The preponderance of evidence suggest that the overall survival results from Study 1 demonstrate a true clinical benefit and are unlikely to be the result of a Type 1 error (false positive probability).

7.0 CLINICAL SAFETY

Sipuleucel-T is safe and well tolerated. The total safety population includes 669 patients who underwent at least 1 leukapheresis. Of these patients, approximately 478 patients received 1387 infusions of sipuleucel-T (note: numbers are estimates due to blinded data and include APC8026, a product similar to sipuleucel-T). The most common AEs were associated with infusion, and these AEs were predominantly transient, not serious, of mild to moderate severity, and did not result in discontinuation of treatment. Only 4 patients out of the 223 patients in the Study 1 and Study 2 safety population did not receive all 3 infusions due to treatment-related AEs.

7.1 Overall Extent of Exposure

The clinical safety profile of sipuleucel-T for the proposed indication is based on the clinical data from 669 patients enrolled in 10 controlled and uncontrolled completed studies (7 studies) or studies currently in progress (3 studies), who were scheduled to be treated with 1 of the following:

- Sipuleucel-T
- Placebo only
- Placebo followed by APC8015F
- APC8026 (a product related to sipuleucel-T, but with a cell processing modification implemented for the isolation of APCs)

All of these studies were conducted in men with metastatic or non-metastatic prostate cancer. The safety population includes all patients who underwent at least 1 leukapheresis procedure and the safety data include all doses of sipuleucel-T administered (typically the maximum manufacturable dose of cells from a single leukapheresis procedure).

There have been 2181 infusions of 1 of the products noted above administered during the clinical trials. Approximately 478 patients have received 1387 infusions of sipuleucel-T (note: numbers

are estimates due to blinded data and include APC8026, a product similar to sipuleucel-T; Table 14).

Table 14 Safety Population, All Clinical Trials

Product	Patients	Infusions
All Cell Products	669	2181
Sipuleucel-T^a	478	1387
Placebo (including APC8015F) ^b	191 ^b	794

^aNumbers are estimates due to blinded data. The numbers for sipuleucel-T include APC8026, a product similar to sipuleucel-T.

^bNumbers are estimates due to blinded data.

In Studies 1 and 2, a total of 223 patients underwent leukapheresis and are included in the safety population. Of the 223 patients in the safety population, 202 patients (90.6%) received all 3 infusions, 15 patients (6.7%) received 2 infusions, and 5 patients (2.2%) received only 1 infusion (Table 15). One patient (0.4%) randomized to the sipuleucel-T group underwent leukapheresis but did not receive any infusions of sipuleucel-T.

Table 15 Number of Patients who received Infusions in Studies 1 and 2 (N = 223^a)

Number of Infusions	Sipuleucel-T (n = 147) n (%)	Placebo (n = 76) n (%)
3	132 (89.8)	70 (92.1)
2	10 (6.8)	5 (6.6)
1	4 (2.7)	1 (1.3)
0	1 (0.7) ^b	0 (0.0)

^aThere are 223 patients in the safety population, which is the number of patients that underwent leukapheresis in Studies 1 and 2.

^bOne patient underwent leukapheresis but did not receive an infusion.

7.2 Integrated Studies 1 and 2

7.2.1 Most Common Adverse Events

The overall incidence of AEs was similar between patients treated with sipuleucel-T (98.6%) compared to patients treated with placebo (96.1%). Those AEs occurring in > 5% of patients treated with sipuleucel-T are shown in Table 16. The most common adverse reactions occurring at a higher rate in those patients treated with sipuleucel-T compared with placebo ($P \leq 0.05$) were chills, pyrexia, headache, asthenia, dyspnea, vomiting, and tremor. These events were primarily Grade 1 and 2. There were no Grade 3 or 4 AEs reported in $\geq 5\%$ of patients in either treatment arm, and p-values for between arm differences in these events were > 0.05 .

Table 16 Adverse Events Occurring in $\geq 5\%$ of Patients Treated with Sipuleucel-T in Studies 1 and 2, by Overall Occurrence and by Occurrence of only Grade 3 or 4 AEs, Number (%) of Safety Population

Preferred Term	Any Grade ^a		Grade 3 or 4 ^a	
	Sipuleucel-T	Placebo	Sipuleucel-T	Placebo
	(n = 147) n (%)	(n = 76) n (%)	(n = 147) n (%)	(n = 76) n (%)
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) ^b	0 (0.0)
Paraesthesia	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)

Preferred Term	Any Grade ^a		Grade 3 or 4 ^a	
	Sipuleucel-T	Placebo	Sipuleucel-T	Placebo
	(n = 147)	(n = 76)	(n = 147)	(n = 76)
	n (%)	n (%)	n (%)	n (%)
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)
Constipation	14 (9.5)	11 (14.5)	1 (0.7)	1 (1.3)
Pain	14 (9.5)	7 (9.2)	1 (0.7)	1 (1.3)
Pain in extremity	14 (9.5)	12 (15.8)	1 (0.7)	0 (0.0)
Anorexia	13 (8.8)	6 (7.9)	0 (0.0)	0 (0.0)
Citrate toxicity	13 (8.8)	6 (7.9)	0 (0.0)	0 (0.0)
Edema peripheral	13 (8.8)	10 (13.2)	0 (0.0)	0 (0.0)
Tremor	13 (8.8)	0 (0.0)	0 (0.0)	0 (0.0)
Myalgia	12 (8.2)	4 (5.3)	0 (0.0)	0 (0.0)
Diarrhea	10 (6.8)	7 (9.2)	0 (0.0)	0 (0.0)
Dizziness	10 (6.8)	4 (5.3)	2 (1.4)	0 (0.0)
Cough	9 (6.1)	6 (7.9)	0 (0.0)	0 (0.0)
Influenza like illness	9 (6.1)	3 (3.9)	0 (0.0)	0 (0.0)
Shoulder pain	9 (6.1)	5 (6.6)	1 (0.7)	0 (0.0)
Upper respiratory tract infection	9 (6.1)	2 (2.6)	0 (0.0)	0 (0.0)
Weight decreased	9 (6.1)	3 (3.9)	0 (0.0)	0 (0.0)
Feeling cold	8 (5.4)	1 (1.3)	0 (0.0)	0 (0.0)
Hematuria	8 (5.4)	3 (3.9)	1 (0.7)	2 (2.6)

^a Severity Grade assessed using National Cancer Institute's Common Toxicity Criteria (version 2.0).

^b All 6 cases of anemia were Grade 3.

Randomization at study entry was 2:1 for sipuleucel-T:placebo.

7.2.1.1 Leukapheresis-related events

The incidences of AEs occurring ≤ 1 day following a leukapheresis procedure and in more than 1 patient are presented in Table 17. The only AE that occurred in $\geq 5\%$ of patients in either treatment arm was paraesthesia (7.5% of patients treated with sipuleucel-T versus 1.3% of patients treated with placebo).

Table 17 Adverse Events Occurring ≤ 1 day following a Leukapheresis Procedure and in More than 1 Patient in Studies 1 and 2, Number (%) of Safety Population

Preferred Term	Sipuleucel-T (n = 147) n (%)	Placebo (n = 76) n (%)
Paraesthesia	11 (7.5)	1 (1.3)
Citrate toxicity	7 (4.8)	3 (3.9)
Muscle spasms	3 (2.0)	2 (2.6)
Back pain	1 (0.7)	3 (3.9)
Fatigue	1 (0.7)	3 (3.9)
Paraesthesia oral	3 (2.0)	1 (1.3)
Arthralgia	2 (1.4)	1 (1.3)
Tremor	3 (2.0)	0 (0.0)
Anemia	2 (1.4)	0 (0.0)
Chest wall pain	1 (0.7)	1 (1.3)
Chills	2 (1.4)	0 (0.0)
Constipation	2 (1.4)	0 (0.0)
Cough	2 (1.4)	0 (0.0)
Pyrexia	1 (0.7)	1 (1.3)

7.2.1.2 Infusion-related events

Those AEs that occurred within 1 day of a product infusion, and that occurred in $\geq 5\%$ of patients in either treatment arm, are summarized in Table 18. Of the AEs that occurred within 1 day of product infusion and in $\geq 5\%$ of patients in either treatment arm, events of chills, pyrexia, headache, tremor, nausea and asthenia all occurred in a higher percentage of patients treated with sipuleucel-T compared to placebo ($P \leq 0.05$).

Table 18 Adverse Events that Occurred ≤ 1 Day Following a Product Infusion and in $\geq 5\%$ of Patients in either Treatment Arm in Studies 1 and 2, Number (%) of Safety Population^a

Preferred Term	Sipuleucel-T (n=145) n (%)	Placebo (n=76) n (%)
Chills	81 (55.9)	3 (3.9)
Fatigue	35 (24.1)	11 (14.5)
Pyrexia	38 (26.2)	2 (2.6)
Headache	20 (13.8)	0 (0.0)
Nausea	17 (11.7)	1 (1.3)
Tremor	12 (8.3)	0 (0.0)
Back pain	7 (4.8)	4 (5.3)
Vomiting	10 (6.9)	1 (1.3)
Asthenia	10 (6.9)	0 (0.0)

^aEvents where the p-values for the between arm differences were ≤ 0.05 are shown in bold.

7.2.2 Adverse Drug Reactions

Three criteria were used to determine those AEs that appear to be potential adverse drug reactions (ADRs) to sipuleucel-T:

- 1) Investigator determined causality
- 2) Difference in the overall incidence of an AE (at any time-point) between treatment arms
- 3) Temporal relationship

Based on these criteria, the following AEs appear to be potential ADRs to sipuleucel-T:

- Chills
- Fatigue
- Asthenia
- Pyrexia
- Headache
- Nausea
- Vomiting
- Dyspnea
- Tremor

Since no treatment differences in AEs occurring 14 or more days after investigational treatment were detected, the AEs that appear potentially related to sipuleucel-T are those that are associated with the infusion of the product. [Table 19](#) indicates that, with the exception of asthenia and dyspnea, the majority of these potentially related ADRs occurred within 1 day of an infusion and occurred considerably less frequently after 14 or more days from last infusion.

Table 19 Potential Adverse Drug Reactions to Sipuleucel-T in Studies 1 and 2, Number (%)^a

Preferred Term	Any Occurrence (n = 147) n (%)	Occurred ≤ 1 Day Following Infusion (n = 145) n (%)	Occurred > 14 Days Following Last Infusion, Through Week 16 (n = 145) n (%)
Chills	85 (57.8)	81 (55.9)	1 (0.7)
Fatigue	63 (42.9)	35 (24.1)	13 (9.0)
Pyrexia	47 (32.0)	38 (26.2)	4 (2.8)
Headache	28 (19.0)	20 (13.8)	3 (2.1)
Nausea	21 (14.3)	17 (11.7)	5 (3.4)
Asthenia	21 (14.3)	10 (6.9)	7 (4.8)
Dyspnea	16 (10.9)	7 (4.8)	7 (4.8)
Vomiting	16 (10.9)	10 (6.9)	3 (2.1)
Tremor	13 (8.8)	12 (8.3)	0 (0.0)

^aPatients with multiple occurrences of the same AE are counted only once for that particular AE, and individual patients could have experienced AEs at more than 1 time-point.

The duration of ADRs that occurred ≤ 1 day following a product infusion and in ≥ 5% of patients in either treatment arm is presented in [Table 20](#). The median duration of each of the common infusion-related AEs was ≤ 2 days.

Table 20 Median Duration (Range) of Adverse Drug Reactions that Occurred ≤ 1 Day Following a Product Infusion in the Sipuleucel-T Treatment Arm in Studies 1 and 2, Number (%)

Preferred Term	Median Duration	(Range)
Chills	35 minutes	(4 minutes to 5 days)
Fatigue	36 hours	(30 minutes to 46 days ^a)
Pyrexia	24 hours	(10 minutes to 3 days)
Headache	81 minutes	(10 minutes to 3 days)
Nausea	24 hours	(10 minutes to 46 days ^a)
Asthenia	48 hours	(24 hours to 46 days ^a)
Dyspnea	62 minutes	(20 minutes to 2 days)
Vomiting	23 minutes	(10 minutes to 3 days)
Tremor	52 minutes	(10 minutes to 2 days)

^aThe events with the longest duration for fatigue, nausea, and asthenia (46 days) all occurred in the same patient with the same start and stop dates.

A small number of the ADRs were Grade 3 or greater in severity, were reported as serious adverse events (SAEs), or led to discontinuation of study treatment ([Table 21](#)).

Table 21 Adverse Drug Reactions to Sipuleucel-T in Studies 1 and 2 that were Judged \geq Grade 3, were Reported as a Serious Adverse Event, or Led to Discontinuation of Study Treatment, Number (%)^a

Preferred Term	All Occurrences of ADRs	ADRs \geq Grade 3	ADRs Reported as SAEs	ADRs that Led to Discontinuation of Infusions
	N = 147	N = 147	N = 147	N = 145
	n (%)	n (%)	n (%)	n (%)
Chills	85 (57.8)	7 (4.8)	5 (3.4)	2 (1.4)
Fatigue	63 (42.9)	2 (1.4)	0 (0.0)	0 (0.0)
Pyrexia	47 (32.0)	3 (2.0)	4 (2.7)	1 (0.7)
Headache	28 (19.0)	2 (1.4)	1 (0.7)	1 (0.7)
Nausea	21 (14.3)	1 (0.7)	1 (0.7)	0 (0.0)
Asthenia	21 (14.3)	0 (0.0)	0 (0.0)	1 (0.7)
Dyspnea	16 (10.9)	5 (3.4)	4 (2.7)	0 (0.0)
Vomiting	16 (10.9)	1 (0.7)	0 (0.0)	0 (0.0)
Tremor	13 (8.8)	0 (0.0)	0 (0.0)	0 (0.0)

^aHighest toxicity grade reported for patients with multiple occurrences of the same AE.

Differences in the incidences of ADRs between patients receiving above the median cumulative number of TNC in sipuleucel-T versus below the median number for Studies 1 and 2 were also analyzed. For the potential ADRs to sipuleucel-T, there was no increased incidence of chills, fatigue, pyrexia, tremor, nausea, dyspnea, asthenia, vomiting, or headache in patients who received a higher TNC dose. There was also no indication of an increased severity for the ADRs in patients who received above the median cumulative CD54⁺ count or CD54 upregulation ratio versus below the median value.

7.2.3 Clinically Important Events

Clinically important events were reviewed in patients that were treated with sipuleucel-T in Studies 1 and 2 (N = 147). Clinically important events were defined as AEs occurring within 24 hours of an infusion of sipuleucel-T that were serious events (i.e., AEs of any grade that required hospitalization) and/or Grade 3 or 4 events.

Clinically important events occurred in 12 of the 147 (8.2%) patients treated with sipuleucel-T (Table 22). The majority of clinically important events were classified as potential ADRs. The events required hospitalization in 5 of 147 patients (3.4%) who were treated with sipuleucel-T and led to discontinuation of therapy in 3 of 147 patients (2.0%). None of these events had a fatal outcome, and in general, the patients recovered within 24 hours and continued with additional sipuleucel-T infusions.

Table 22 Clinically Important Events Reported in Patients treated with Sipuleucel-T in Studies 1 and 2, Number of Patients (%)^a

Preferred Term	N = 147 n (%)
Patients with Clinically Important Events	12 (8.2)
Chills	6 (4.1)
Headache	2 (1.4)
Hypoxia	2 (1.4)
Pyrexia	1 (0.7)
Nausea	1 (0.7)
Vomiting	1 (0.7)
Other ^b	8 (5.4)

^aClinically important events defined as adverse events occurring within 24 hours of infusion that were Grade 3 or 4 in severity or led to hospitalization.

^bEight patients experienced 1 or more of the following events: dizziness and hypertension (in 2 patients each); and blood in urine, anemia, chest discomfort, nail discoloration (blanching), bilateral flank pain, back pain, chest wall pain, paraesthesia, cyanosis, and pallor (in 1 patient each).

There were 2 patients with clinically important respiratory events (defined as Grade 3 or 4 events or events that led to hospitalization within 24 hours of infusion). One 80-year-old patient experienced Grade 3 hypoxia, required hospitalization for 1 day, and he also had a history of pulmonary disease. This patient discontinued treatment with sipuleucel-T due to the respiratory event and did not receive his third infusion of sipuleucel-T. The remaining 76-year-old patient experienced Grade 3 hypoxia on his second infusion, but he did not experience recurrence of hypoxia on his third infusion. Both patients recovered without sequelae.

7.2.4 Deaths

Given that the median life expectancy of men with metastatic AIPC is less than 2 years, death was an expected outcome in these studies. In the safety population of Studies 1 and 2, a total of 67% of patients treated with sipuleucel-T and 84% of patients treated with placebo died during the 3-year reporting period. The majority of the deaths were attributed to disease progression. There were no deaths attributed to the study product as assessed by the clinical Investigators.

7.2.5 Serious Adverse Events

The frequency of SAEs in Studies 1 and 2 was similar between patients treated with sipuleucel-T and placebo (23.8% versus 22.4%, respectively). No SAEs (by preferred term) were reported in $\geq 5\%$ of patients in either treatment arm ([Table 23](#)). The following SAEs were the most commonly reported SAEs in patients treated with sipuleucel-T:

- Chills (5 patients, 3.4%)
- Dyspnea (4 patients, 2.7%)
- Pyrexia (4 patients, 2.7%)
- Cerebrovascular accident (3 patients, 2.0%)
- Dehydration (3 patients, 2.0%)

Serious adverse events in 27 of 35 patients treated with sipuleucel-T who experienced SAEs (77.1%) and 13 of 17 patients treated with placebo who experienced SAEs (76.5%) were judged by the Investigator to be unrelated to study treatment, and most of these SAEs were related to disease progression or comorbidities seen in this patient population.

Table 23 **Summary of Serious Adverse Events Occurring in More than 1 Patient in Studies 1 and 2 by Preferred Term, Number (%) of Safety Population**

Preferred Term	Sipuleucel-T	Placebo
	(n = 147) n (%)	(n = 76) n (%)
Chills	5 (3.4)	0 (0.0)
Dehydration	3 (2.0)	2 (2.6)
Dyspnea	4 (2.7)	1 (1.3)
Urinary retention	2 (1.4)	3 (3.9)
Hematuria	2 (1.4)	2 (2.6)
Pyrexia	4 (2.7)	0 (0.0)
Back pain	2 (1.4)	1 (1.3)
Cerebrovascular accident	3 (2.0)	0 (0.0)
Sepsis	2 (1.4)	1 (1.3)
Bacteremia	1 (0.7)	1 (1.3)
Cardiac failure congestive	1 (0.7)	1 (1.3)
Catheter sepsis	2 (1.4)	0 (0.0)
Chest wall pain	2 (1.4)	0 (0.0)
Deep vein thrombosis	0 (0.0)	2 (2.6)
Hypertension	2 (1.4)	0 (0.0)
Pain	1 (0.7)	1 (1.3)
Pathological fracture	1 (0.7)	1 (1.3)
Spinal cord compression	2 (1.4)	0 (0.0)
Urinary tract infection	2 (1.4)	0 (0.0)

7.2.6 Additional Safety Observations

In addition to the AEs described above, safety data were reviewed for the following events considered of clinical interest:

- Catheter-related infections
- Autoimmune events
- Second malignancies
- Cerebrovascular events

Catheter-related Infections

Some patients require placement of in-dwelling catheters to provide adequate venous access. Infections that were potentially attributed to all types of venous catheters used for study purposes were reviewed in Studies 1 and 2. There were 10 of 223 patients (4.5%) who experienced AEs consistent with catheter-related infections that occurred following any leukapheresis or infusion. Nine of the AEs were Grade 3 in severity and 1 event was Grade 4. In 1 patient, the Grade 3 catheter-related infection was still ongoing when the patient went off-study for the primary endpoint; all of the other catheter-related infections resolved with appropriate management, which included antibiotic therapy.

Autoimmune Events

The risk of autoimmune events is of concern when patients receive various types of immunotherapy for malignancies, such as interferon-alpha, interleukin-2, and rituximab. A thorough review of AEs classified as autoimmune events (and including other inflammatory conditions which could be attributable to infectious or other etiologies) was performed for Studies 1 and 2. Based on this review, there does not appear to be any evidence of such events occurring more frequently following treatment with sipuleucel-T ([Table 24](#)). All patients who experienced events that were classified as autoimmune events also had relevant contributory risk factors or comorbidity associated with the events. None of these events were attributed to treatment with sipuleucel-T.

Table 24 Summary of Potential Autoimmune Events in Studies 1 and 2, Number (%) of Safety Population

Preferred Term	Sipuleucel-T N=147	Placebo N=76
Any Potential Autoimmune Adverse Event	8 (5.4%)	5 (6.6%)
Alopecia	1 (0.7%)	0 (0.0%)
Aphthous stomatitis	0 (0.0%)	1 (1.3%)
Arthritis	1 (0.7%)	1 (1.3%)
Cellulitis	0 (0.0%)	1 (1.3%)
Cystitis	1 (0.7%)	0 (0.0%)
Dermatitis	1 (0.7%)	0 (0.0%)
Dermatitis contact	1 (0.7%)	0 (0.0%)
Folliculitis	0 (0.0%)	1 (1.3%)
Gastritis	2 (1.4%)	0 (0.0%)
Pernicious anemia	1 (0.7%)	0 (0.0%)
Prostatitis	0 (0.0%)	1 (1.3%)

Second Malignancies

Second malignancies were also evaluated in Studies 1 and 2. There was no evidence that second malignancies developed in a higher percentage of patients treated with sipuleucel-T versus placebo. There were 4 occurrences of second malignancies in 147 patients (2.7%) treated with sipuleucel-T and 2 occurrences in 76 patients (2.6%) treated with placebo. Furthermore, there was no evidence that a specific category or type of malignancy developed following treatment with either sipuleucel-T or placebo; the cases of second cancers that occurred in these studies were varied in cell type as well as primary anatomic site.

Cerebrovascular Events

A review of cerebrovascular event data in Studies 1 and 2 revealed a possible increased risk in patients treated with sipuleucel-T. In order to thoroughly evaluate this risk, all randomized Phase III studies conducted to date were reviewed; therefore, in addition to Studies 1 and 2, the review also included data from the ongoing Study P-11 (N = 175) and Study 3 (N = 294). Study 3 data were provided by the Independent Data Monitoring Committee (IDMC), without

unblinding at the patient level, for all patients who have undergone at least 1 leukapheresis procedure. Safety data for the non-randomized Phase I and II studies were also reviewed.

For all randomized studies conducted to date, the incidence of cerebrovascular events of any etiology was 3.9% in patients treated with sipuleucel-T (18 of 461 patients) compared to 2.6% in patients treated with placebo (6 of 231 patients; Table 25). The odds ratio (OR) for risk of stroke in the sipuleucel-T arm relative to the control arm is 1.52, with the 95% CI overlapping 1.00 ([95% CI: 0.60, 3.89]; $P = 0.510$). The incidence of hemorrhagic events was 0.7% in patients treated with sipuleucel-T compared to 0.4% in patients treated with placebo, and the incidence of ischemic events was 2.4% compared to 2.2%, respectively. Four cerebrovascular events in patients treated with sipuleucel-T were of unknown etiology (0.9%). The majority of these cerebrovascular events were not fatal, with 1.5% and 0.9% of the events resulting in death (OR = 1.76 [95% CI: 0.36, 8.57]; $P = 0.725$).

No cerebrovascular events were reported in the 101 patients treated in non-randomized studies of sipuleucel-T (and APC8026) to date; and no events have been reported in the 100 patients treated with APC8015F on the salvage protocols, Studies D9903 and PB01.

Table 25 Incidence of Cerebrovascular Events, All Randomized Studies^a

	Sipuleucel-T N=461	Placebo N=231	Odds Ratio (95% CI)	P-value ^b
All Events	3.9%	2.6%	1.52 (0.60, 3.89)	0.510
Hemorrhagic	0.6%	0.4%	1.51 (0.16, 14.56)	1.000
Ischemic	2.4%	2.2%	1.10 (0.38, 3.22)	1.000
Unknown	0.9%	0.0%	Not Applicable	0.307
Deaths	1.5%	0.9%	1.76 (0.36, 8.57)	0.725

^aIncludes Studies 1, 2, 3, and P-11

^bFisher's exact test

Patients who experienced cerebrovascular events had increased stroke risk factors compared to those who did not experience cerebrovascular events in the study population. A correlation between cumulative cell dose and the occurrence of cerebrovascular event has not been

established. The incidence of cerebrovascular events observed in patients treated with sipuleucel-T is comparable to that seen in men with advanced prostate cancer based on an analysis of 5 years of data from a SEER-Medicare linked database.

An analysis of non-neurologic vascular events of all types was performed in all randomized Phase III studies. There has been no evidence of any type of vascular event outside of the central nervous system occurring more frequently in patients treated with sipuleucel-T, including no evidence of myocardial infarction, angina, pulmonary embolism, or venous thromboses.

Given the large p-values and wide CIs, the lack of clear association with ischemic or hemorrhagic etiology, the lack of correlation with cell dose, the high underlying rate of stroke in this patient population, and the absence of an increased incidence of non-neurologic events, there is no conclusive evidence at the present time to associate sipuleucel-T with an increased risk of cerebrovascular events.

7.3 Integrated Summary of Key Common Adverse Events (Potential Adverse Drug Reactions to Sipuleucel-T) for All Studies

Based on the frequency of AEs reported in patients treated with sipuleucel-T versus patients treated with placebo in the completed, randomized and double blind studies, as well as evaluation of the temporal relationship between the AEs and the time of infusion of sipuleucel-T across all clinical studies, the following AEs appear to be ADRs to sipuleucel-T: chills, fatigue and asthenia, pyrexia, headache, nausea and vomiting, dyspnea, and tremor ([Table 26](#)). Even with the limitations of including blinded data and different product formulations (sipuleucel-T, APC8015F, or APC8026) there is a consistency in the AE profile across the randomized and non-randomized studies. The majority of the ADRs were 1) judged by the Investigator to be treatment-related, 2) occurred within 1 day of an infusion, 3) resolved within 24 hours, and 4) occurred considerably less frequently after 14 or more days from last infusion. Few of these ADRs were Grade 3 or greater in severity, were reported as SAEs, or led to discontinuation of study treatment.

Table 26 Potential Adverse Drug Reactions by Type of Study Product Received, All Studies^a

Preferred Term	Sipuleucel-T n = 233 n (%)	Placebo ^b n = 76 n (%)	Either Sipuleucel-T or Placebo ^{b,c} n = 345 n (%)	Placebo followed by APC8015F n = 81 n (%)	APC8026 n = 15 n (%)
Chills (rigors)	125 (53.6)	6 (7.9)	118 (34.2)	14 (17.3)	9 (60.0)
Fatigue	88 (37.8)	22 (28.9)	123 (35.7)	14 (17.3)	3 (20.0)
Pyrexia (fever)	73 (31.3)	5 (6.6)	79 (22.9)	9 (11.1)	4 (26.7)
Headache	39 (16.7)	5 (6.6)	54 (15.7)	1 (1.2)	1 (6.7)
Nausea	38 (16.3)	6 (7.9)	53 (15.4)	12 (14.8)	3 (20.0)
Asthenia (weakness)	31 (13.3)	3 (3.9)	26 (7.5)	6 (7.4)	2 (13.3)
Dyspnea	26 (11.2)	2 (2.6)	21 (6.1)	4 (4.9)	1 (6.7)
Vomiting	25 (10.7)	2 (2.6)	21 (6.1)	5 (6.2)	1 (6.7)
Tremor	19 (8.2)	0 (0.0)	13 (3.8)	1 (1.2)	1 (6.7)

^aPatients with multiple occurrences of the same AE are counted only once for that particular AE.

^bPatients treated with placebo could also be treated with APC8015F.

^cTreatment is blinded.

7.4 Safety Conclusions

The known ADRs to sipuleucel-T demonstrate a favorable safety profile that is consistent across all studies. The most frequent events have been chills, pyrexia, and fatigue similar to the infusion reactions observed with other IV immunotherapies. These events were generally mild to moderate in severity, were treated on an outpatient basis, and resolved within a few days. An increased incidence of cerebrovascular events has been observed in the sipuleucel-T arm relative to the placebo arm in some studies. This incidence is associated with a large p-value and a wide confidence interval. Thus, there is no conclusive evidence at the present time to associate sipuleucel-T with an increased risk of cerebrovascular events. Few patients (only 4 patients from the integrated studies) were unable to tolerate all infusions of sipuleucel-T due to toxicities.

8.0 RISKS AND BENEFITS

The primary benefit of treatment with sipuleucel-T is an increased overall survival based on all randomized patients in 2 randomized, double blind, multicenter, and placebo-controlled studies. It is well tolerated with a short duration of treatment and a favorable safety profile. The known risks are well characterized. The most common AEs are associated with infusion. They are generally transient, non-serious, mild to moderate, and do not result in treatment discontinuation.

8.1 Risks

The known risks associated with sipuleucel-T treatment have been well characterized in 669 patients enrolled in controlled and uncontrolled studies. Of the known treatment-related risks, the most frequent are chills, fatigue, asthenia, fever, headache, nausea, vomiting, dyspnea, and tremor. These events are modest in severity, most commonly associated with the infusion, and may be controlled with acetaminophen and diphenhydramine. In rare cases, these events may be serious and typically these infusion-related events are of short duration and resolve with treatment. The potential risks associated with sipuleucel-T treatment include the following:

- Risks specific to the autologous nature of this product. In some cases, in-dwelling catheters are used to provide adequate venous access. These catheters require proper maintenance to avoid infection. Other process-related risks include: 1) the possibility that a product may not be able to be produced from a given patient's leukapheresis; and 2) the logistical risks involving the timely delivery of the leukapheresis to Dendreon followed by the timely delivery of activated cells back to the patient. These risks are mitigated through training, tight controls, and advanced logistics solutions.
- Clinical trial experience to date in randomized studies suggests a possible increased risk of cerebrovascular events. The incidence appears consistent with that seen in men of advanced age with cancer and other risk factors. Thus, there is no conclusive evidence at the present time to associate sipuleucel-T with an increased risk of cerebrovascular events.

In the context of advanced prostate cancer these risks are very well balanced against the demonstrated benefits of sipuleucel-T treatment.

8.2 Benefits

The benefits of treatment with sipuleucel-T include the following:

- Clinically significant prolongation of overall survival;
- Short treatment duration and high patient compliance rate;
- Favorable safety profile; and
- Treatment does not appear to preclude the use of other subsequent therapies such as chemotherapy.

8.3 Risks and Benefits Conclusions

Sipuleucel-T represents an important advance in the treatment of AIPC and, if approved, will provide physicians and patients with the option of a new therapy that is well tolerated and extends overall survival.

9.0 OVERALL CONCLUSIONS

Sipuleucel-T prolongs survival in patients with asymptomatic metastatic AIPC. Treatment with sipuleucel-T is well tolerated and has well characterized and manageable known risks.

In Study 1, the survival results are clinically meaningful, statistically persuasive, and internally consistent. Multiple sensitivity analyses confirm the treatment benefit. The survival advantage observed in Study 1 is further supported by a strong trend toward a delay in TTP in Study 1, a trend toward prolonged survival in Study 2, and the survival results of the integrated analysis of Studies 1 and 2.

The findings are further supported by the strong correlation observed between overall survival and the cumulative CD54 upregulation product release values for sipuleucel-T.

The safety and tolerability of treatment with sipuleucel-T should increase patient acceptance and compliance, making sipuleucel-T an important option for the treatment of asymptomatic metastatic AIPC.

10.0 REFERENCES

Akimoto S, Furuya Y, Akakura K, et al. Inability of bone turnover marker as a strong prognostic indicator in prostate cancer patients with bone metastasis: comparison with the extent of disease (EOD) grade. *Prostate* 1999;38(1):28-34.

Burch PA, Breen JK, Buckner JC, et al. Priming tissue-specific cellular immunity in a phase I trial of autologous dendritic cells for prostate cancer. *Clin Cancer Res* 2000;6(6):2175-82.

Burch PA, Croghan GA, Gastineau DA, et al. Immunotherapy (APC8015, Provenge) targeting prostatic acid phosphatase can induce durable remission of metastatic androgen-independent prostate cancer: a Phase 2 trial. *Prostate* 2004;60(3):197-204.

Collette L, van Andel G, Bottomley A, et al. Is baseline quality of life useful for predicting survival with hormone-refractory prostate cancer? A pooled analysis of three studies of the European Organisation for Research and Treatment of Cancer Genitourinary Group. *J Clin Oncol* 2004;22(19):3877-85.

Crawford ED, Eisenberger MA, McLeod DG, et al. A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. *N Engl J Med* 1989;321(7):419-24.

Dagher R, Li N. Clinical review for NDA 20-449/S-028 (Taxotere[®] [docetaxel]): Department of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Drug Evaluation and Research; 2004 19 MAY 2004.

Dawson NA, Conaway M, Halabi S, et al. A randomized study comparing standard versus moderately high dose megestrol acetate for patients with advanced prostate carcinoma: cancer and leukemia group B study 9181. *Cancer* 2000;88(4):825-34.

DeWys WD, Begg CB, Brodovsky H, et al. A comparative clinical trial of adriamycin and 5-fluorouracil in advanced prostatic cancer: prognostic factors and response. *Prostate* 1983;4(1):1-11.

Docetaxel Product Label. Product label: Taxotere (docetaxel): Aventis Pharmaceuticals, Inc.; 2005.

Emrich LJ, Priore RL, Murphy GP, et al. Prognostic factors in patients with advanced stage prostate cancer. *Cancer Res* 1985;45(10):5173-9.

Fossa SD, Paus E, Lindegaard M, et al. Prostate-specific antigen and other prognostic factors in patients with hormone-resistant prostatic cancer undergoing experimental treatment. *Br J Urol* 1992;69(2):175-9.

Gerloni M, Zanetti M. CD4 T cells in tumor immunity. *Springer Semin Immunopathol* 2005;27(1):37-48.

Halabi S, Small EJ, Kantoff PW, et al. Prognostic model for predicting survival in men with hormone-refractory metastatic prostate cancer. *J Clin Oncol* 2003;21(7):1232-7.

Ibrahim A, Johnson J. FDA clinical briefing document for the oncologic drug advisory committee September 13, 2005 meeting. Briefing Document: Department of Health and Human

Services, Public Health Service, Food and Drug Administration, Center for Drug Evaluation and Research; 2005 13 SEP.

Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2007. *CA Cancer J Clin* 2007;57(1):43-66.

Kelly WK, Scher HI, Mazumdar M, et al. Prostate-specific antigen as a measure of disease outcome in metastatic hormone-refractory prostate cancer. *J Clin Oncol* 1993;11(4):607-15.

Kirk TN, Kiefert J, Moyad MA. National survey of HRPc patients reveals large gaps between perceptions and reality of treatment. *Proc Prostate Cancer Symposium 2006*:Abstract 222.

Knutson KL, Disis ML. Tumor antigen-specific T helper cells in cancer immunity and immunotherapy. *Cancer Immunol Immunother* 2005;54(8):721-8.

Laus R, Yang DM, Ruegg CL, et al. Dendritic cell immunotherapy of prostate cancer: Preclinical models and early clinical experience. *Cancer Research Therapy and Control* 2001;11:1-10.

Petrylak DP, Scher HI, Li Z, et al. Prognostic factors for survival of patients with bidimensionally measurable metastatic hormone-refractory prostatic cancer treated with single-agent chemotherapy. *Cancer* 1992;70(12):2870-8.

Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* 2004;351(15):1513-20.

Saad F, Gleason DM, Murray R, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst* 2002;94(19):1458-68.

Schellhammer PF, Venner P, Haas GP, et al. Prostate specific antigen decreases after withdrawal of antiandrogen therapy with bicalutamide or flutamide in patients receiving combined androgen blockade. *J Urol* 1997;157(5):1731-5.

Scher HI, Kelly WK. Flutamide withdrawal syndrome: its impact on clinical trials in hormone-refractory prostate cancer. *J Clin Oncol* 1993;11(8):1566-72.

Scher HI, Kelly WM, Zhang ZF, et al. Post-therapy serum prostate-specific antigen level and survival in patients with androgen-independent prostate cancer. *J Natl Cancer Inst* 1999;91(3):244-51.

Scholz M, Jennrich R, Strum S, et al. Long-term outcome for men with androgen independent prostate cancer treated with ketoconazole and hydrocortisone. *J Urol* 2005;173(6):1947-52.

Smaletz O, Scher HI, Small EJ, et al. Nomogram for overall survival of patients with progressive metastatic prostate cancer after castration. *J Clin Oncol* 2002;20(19):3972-82.

Small EJ, Fratesi P, Reese DM, et al. Immunotherapy of hormone-refractory prostate cancer with antigen-loaded dendritic cells. *J Clin Oncol* 2000;18(23):3894-903.

Small EJ, Halabi S, Ratain MJ, et al. Randomized study of three different doses of suramin administered with a fixed dosing schedule in patients with advanced prostate cancer: results of intergroup 0159, cancer and leukemia group B 9480. *J Clin Oncol* 2002;20(16):3369-75.

Small EJ, Srinivas S. The antiandrogen withdrawal syndrome. Experience in a large cohort of unselected patients with advanced prostate cancer. *Cancer* 1995;76(8):1428-34.

Soloway MS, Ishikawa S, van der Zwaag R, et al. Prognostic factors in patients with advanced prostate cancer. *Urology* 1989;33(5 Suppl):53-6.

Tang S, Sridhara R, Mahjoob K, et al. 10 mg Atrasentan (NDA/Serial Number 21-491): U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation Research, Office of Pharmacoepidemiology and Statistical Science, Office of Biostatistics; 2005 15 AUG 2005.

Vollmer RT, Dawson NA, Vogelzang NJ. The dynamics of prostate specific antigen in hormone refractory prostate carcinoma: an analysis of cancer and leukemia group B study 9181 of megestrol acetate. *Cancer* 1998;83(9):1989-94.

Vollmer RT, Kantoff PW, Dawson NA, et al. A prognostic score for hormone-refractory prostate cancer: analysis of two cancer and leukemia group B studies. *Clin Cancer Res* 1999;5(4):831-7.

Ward JF, Moul JW. Rising prostate-specific antigen after primary prostate cancer therapy. *Nat Clin Pract Urol* 2005;2(4):174-82.

Wyatt RB, Sanchez-Ortiz RF, Wood CG, et al. Prognostic factors for survival among Caucasian, African-American and Hispanic men with androgen-independent prostate cancer. *J Natl Med Assoc* 2004;96(12):1587-93.

APPENDIX 1 TABULAR SUMMARY OF ALL CLINICAL STUDIES

Type of Study	Study Identifier	Measures of Safety and Efficacy	Study Design; Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Patients (sipuleucel-T: placebo)	Healthy Patients or Diagnosis of Patients	Duration of Treatment
Controlled Clinical Studies Pertinent to the Claimed Indication							
Phase III; Safety and Efficacy	Study 1 (D9901)	<ul style="list-style-type: none"> Survival TTP TDRP Response rate and duration of response Immune response Safety of sipuleucel-T 	Double blind, multicenter, randomized (2:1); Placebo-controlled	Sipuleucel-T or placebo; 3 autologous doses, each dose the maximum that could be prepared from a single leukapheresis (minimum 3×10^6 CD54 ⁺ cells); IV infusion	127 (82:45)	Asymptomatic, metastatic, androgen independent prostate cancer (AIPC)	Approximately 4 weeks, with 1 dose given in Weeks 0, 2, and 4
Phase III; Safety and Efficacy	Study 2 (D9902A)	<ul style="list-style-type: none"> Survival TTP TDRP Response rate and duration of response Safety of sipuleucel-T 	Double blind, multicenter, randomized (2:1); Placebo-controlled	Sipuleucel-T or placebo; 3 autologous doses, each dose the maximum that could be prepared from a single leukapheresis (minimum 3×10^6 CD54 ⁺ cells); IV infusion	98 (65:33)	Asymptomatic, metastatic, AIPC	Approximately 4 weeks, with 1 dose given in Weeks 0, 2, and 4

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Patients	Healthy Patients or Diagnosis of Patients	Duration of Treatment
Uncontrolled Clinical Studies							
Phase I/II; Safety	9610	<ul style="list-style-type: none"> • Safety of sipuleucel-T • Immune response • Tumor response 	Open-label, dose escalation; No control	Sipuleucel-T; 3 dose level cohorts: 1) 0.2×10^9 cells/m ² 2) 0.6×10^9 cells/m ² 3) 1.2×10^9 cells/m ² ; IV infusion	Phase I: 12 Phase II: 19	Phase I: Metastatic AIPC Phase II: Non-Metastatic AIPC	Approximately 24 weeks, with 1 dose given in Weeks 0, 4, 8 and 24

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Patients	Healthy Patients or Diagnosis of Patients	Duration of Treatment
Uncontrolled Clinical Studies (Continued)							
Phase I/II; Safety	9702	<ul style="list-style-type: none"> • Safety of sipuleucel-T and PA2024 • Immune response • Tumor response 	Open-label, dose escalation; No control	<p>Sipuleucel-T; Approximately 1.2×10^9 nucleated cells/m²; IV infusion</p> <p>PA2024; Phase I: 3 dose level cohorts: 1) 0.3 mg 2) 0.6 mg 3) 1.0 mg; Phase II: 1.0 mg; Subcutaneous (s.c.) injection</p>	<p>Phase I: 13</p> <p>Phase II: 21</p>	Metastatic AIPC	<p>Phase I: Approximately 16 weeks, with one IV dose given in Weeks 0 and 4 and s.c. antigen injections given at Weeks 8, 12, and 16</p> <p>Phase II: Approximately 12 weeks, with one IV dose given in Weeks 0 and 2 and s.c. antigen injections given at Weeks 4, 8, and 12</p>

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Patients	Healthy Patients or Diagnosis of Patients	Duration of Treatment
Uncontrolled Clinical Studies (Continued)							
Phase II; Safety	D9903	<ul style="list-style-type: none"> • Safety of APC8015F • Response rate and duration • TTP 	Open-label, multicenter, salvage; No control	APC8015F; 3 autologous cell doses, each dose prepared from cryopreserved PBMCs, including APCs, (minimum 3×10^6 CD54 ⁺ cells); IV infusion	56	AIPC patients with objective disease progression following participation in the placebo arm of Studies 1 or 2	Approximately 4 weeks, with 1 dose given in Weeks 0, 2, and 4

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Patients	Healthy Patients or Diagnosis of Patients	Duration of Treatment
Other Clinical Studies – Completed Studies							
Phase II; Safety	D9905	<ul style="list-style-type: none"> • Safety of sipuleucel-T • Tumor response • TTP 	Open-label; No control	Sipuleucel-T; 3 autologous doses, each dose the maximum that could be prepared from a single leukapheresis (approximately 1.2×10^9 cells/m ²); IV infusion	18	Non-metastatic prostate cancer with PSA progression after definitive local therapy	Approximately 4 weeks, with 1 dose given in Weeks 0, 2, and 4
Phase I; Safety	D9801	<ul style="list-style-type: none"> • Safety of APC8026 • Immune response • Relationship between cell dose and immune response 	Open-label; No control	APC8026; 3 dose level cohorts: 1) 1.0×10^9 cells/ m ² 2) 2.5×10^9 cells/m ² 3) 4.0×10^9 cells/m ² ; IV infusion	15	Advanced AIPC	Approximately 16 weeks, with 1 dose given in Week 0, 2, 4, and 16

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Patients	Healthy Patients or Diagnosis of Patients	Duration of Treatment
Other Clinical Studies – Ongoing Studies							
Phase III; Safety and Efficacy	P-11	<ul style="list-style-type: none"> • Time to PSA \geq 3 ng/mL • Time to distant failure • Survival • Safety of sipuleucel-T 	Double blind, multicenter, randomized (2:1); Placebo-controlled	Sipuleucel-T or placebo; 3 autologous cell doses, each dose the maximum that could be prepared from a single leukapheresis (minimum 3×10^6 CD54 ⁺ cells prior to DEC 2003 or 20×10^6 CD54 ⁺ cells thereafter); IV infusion	176	Non-metastatic, prostate cancer with PSA progression following radical prostatectomy	Approximately 4 weeks, with 1 dose given in Weeks 0, 2, and 4. An optional booster (sipuleucel-T or placebo per original randomization) is available at time of PSA progression
Phase III; Safety and Efficacy	Study 3 (D9902B)	<ul style="list-style-type: none"> • Survival • TTP • Safety of sipuleucel-T 	Double blind, multicenter, randomized (2:1); Placebo-controlled	Sipuleucel-T or placebo; 3 autologous doses, each dose the maximum that could be prepared from a single leukapheresis (minimum 20×10^6 CD54 ⁺ cells); IV infusion	179 (as of 06 FEB 2006)	Asymptomatic or minimally symptomatic, metastatic, AIPC	Approximately 4 weeks, with 1 dose given in Weeks 0, 2, and 4

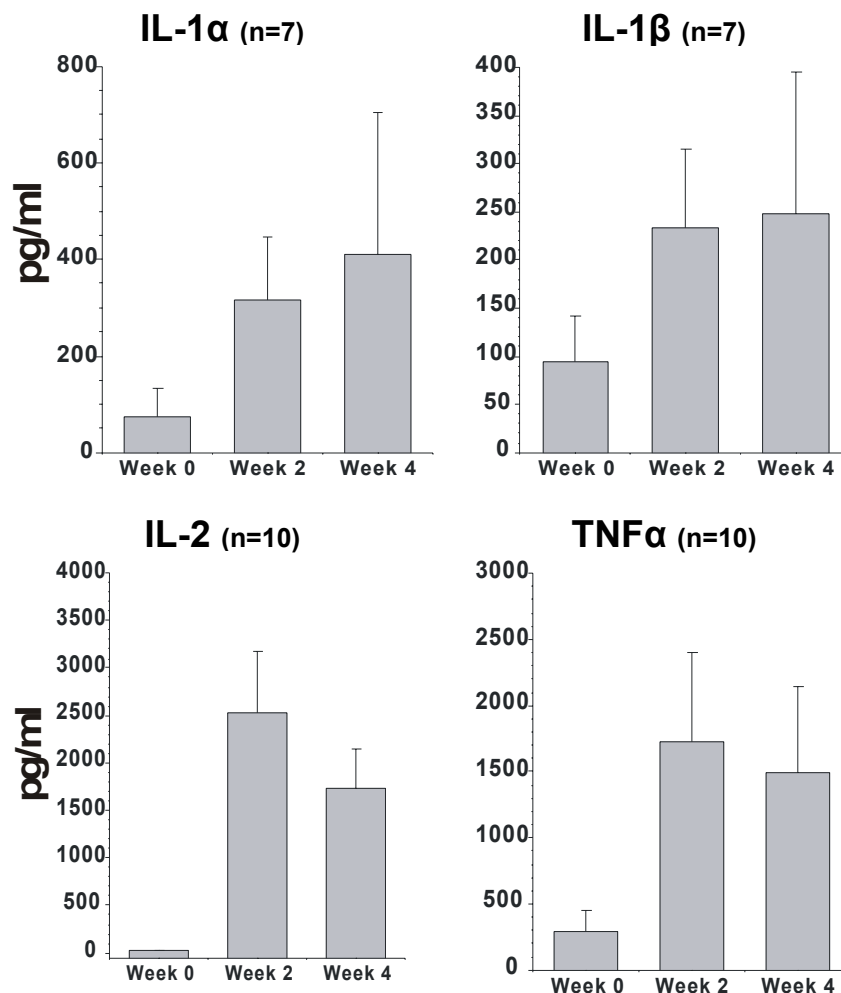
Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Patients	Healthy Patients or Diagnosis of Patients	Duration of Treatment
Other Clinical Studies – Ongoing Studies (Continued)							
Phase II; Safety	PB01	<ul style="list-style-type: none"> • Safety of APC8015F • Change in prostate-specific antigen doubling time (PSADT) • Overall response 	Open-label, multicenter, salvage; No control	APC8015F; 3 autologous cell doses, each dose prepared from cryopreserved PBMCs, including APCs (minimum 3×10^6 CD54 ⁺ cells); IV infusion	28 (as of 31 JAN 2006)	AIPC patients with objective disease progression following participation in the placebo arm of Study 3	Approximately 4 weeks, with 1 dose given in Weeks 0, 2, and 4

APPENDIX 2 SUMMARY OF T CELL AND NK CELL ACTIVATION

Cytokine Secretion Indicates General Immune Activation

Cytokines are secreted cell signaling molecules that provide a means of communication between cells of the immune system. For example, T cells and APCs can be induced to secrete cytokines upon activation. To determine how cytokine secretion during culture changes from treatment to treatment, samples of post-culture medium were collected during the manufacture of Week 0, Week 2, and Week 4 treatments for a series of patients. These samples were assayed for a variety of cytokines. [Figure 35](#) shows the levels of selected cytokines in the post-culture supernatants (for each cytokine, the number of patient data sets is shown). IL-1 α and IL-1 β are produced by activated APCs, while IL-2 and tumor necrosis factor alpha (TNF α) are associated with T-cell activation. The levels of these cytokines in the post-culture medium increased after the initial treatment with sipuleucel-T. Similar results were obtained for 9 additional cytokines, IL-3, IL-4, IL-5, IL-8, IL-10, IL-17, IL-23, IP-10, and interferon-gamma (IFN γ). These results show that 1) the different cell types in sipuleucel-T can interact during ex vivo culture, and 2) sipuleucel-T treatment increases the extent of these interactions, suggesting a possible activation of both innate and adaptive arms of the immune system.

Figure 35 Cytokine Production during Ex Vivo Culture



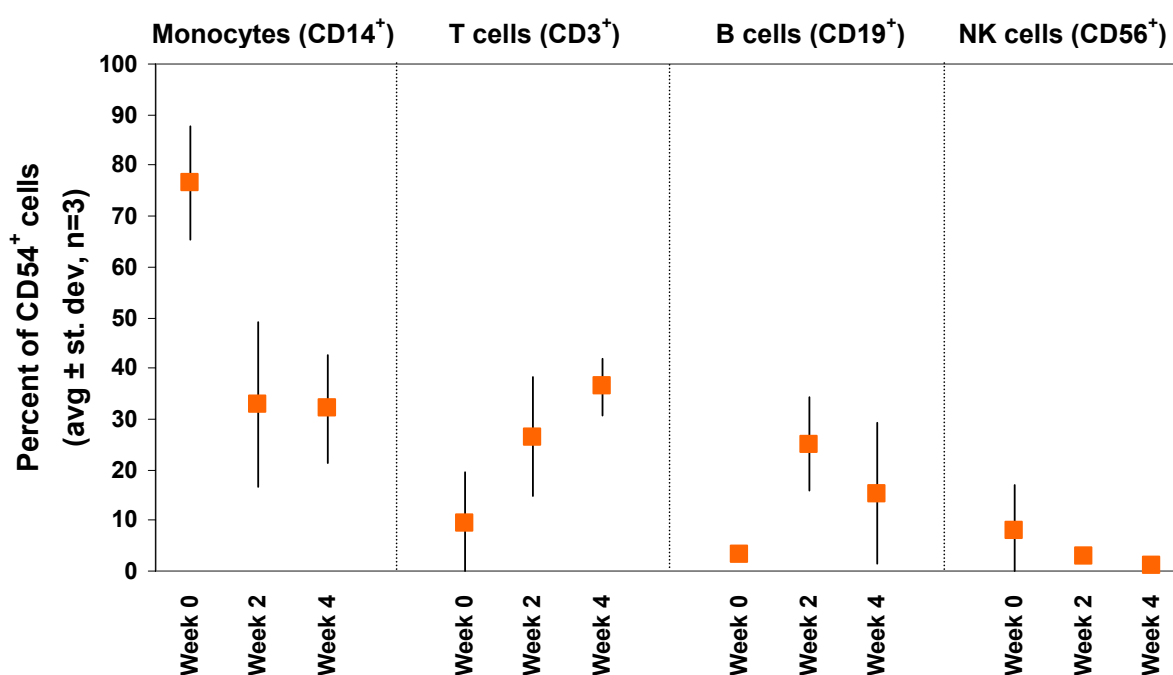
T cell Activation in Sipuleucel-T

CD54 is expressed on the surface of other activated immune cells besides APCs. [Figure 36](#) shows how the composition of the overall CD54⁺ cell population in sipuleucel-T changed over the course of treatment for 3 prostate cancer patients (average \pm standard deviation). At Week 0, the CD54⁺ cell population consisted primarily of monocyte-derived APCs, and contained relatively few T cells, B cells, or NK cells. At Weeks 2 and 4, the percentage of monocytes in the total CD54⁺ cell population decreased, and the percentage of T cells increased. By Week 4, the average percentage of T cells in the CD54⁺ cell population exceeded the average percentage of monocytes. Through all these treatments, cell numbers remained steady, indicating that the

percentage of T cells in the CD54⁺ cell population increased due to T cell activation. These results show that sipuleucel-T prepared for Week 2 and Week 4 treatments contains activated T cells.

(The increase in CD54 expression by T cells does not affect sipuleucel-T product potency as measured by APC CD54 upregulation, which is calculated for the large CD54⁺ cell population. Smaller cells such as T cells are excluded from the APC CD54 upregulation calculation.)

Figure 36 Composition of the CD54⁺ Cell Population in Sipuleucel-T over Successive Treatments



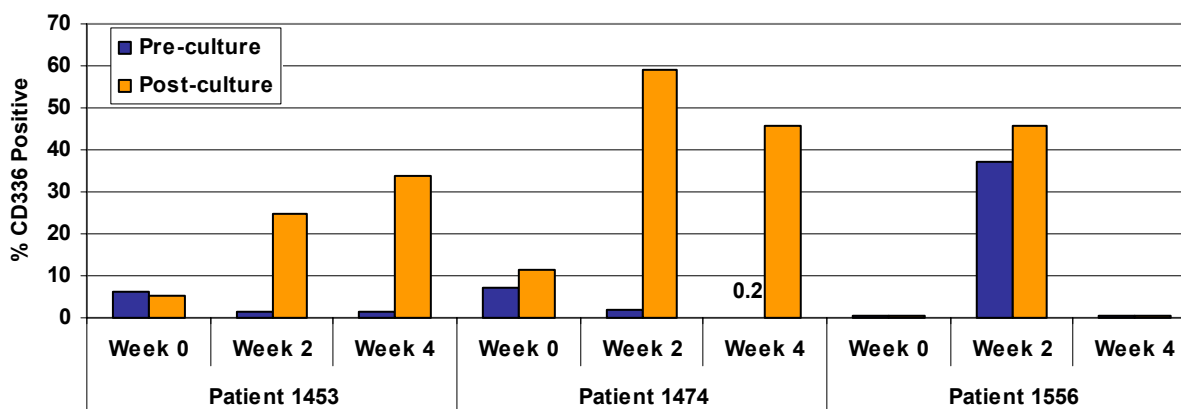
NK Cells are Activated and Acquire Lytic Activity

Changes in cytokine production over the course of sipuleucel-T treatments suggest the innate immune system is activated. Additional experiments have evaluated the activation and lytic activity of the NK cells. (As shown in [Figure 20](#), NK cells typically comprise less than 15% of the nucleated cells in sipuleucel-T.)

CD336 is expressed by NK cells upon activation. [Figure 37](#) shows that NK cells in Week 0 treatments were not activated during ex vivo culture with PA2024. For 2 patients, activation of

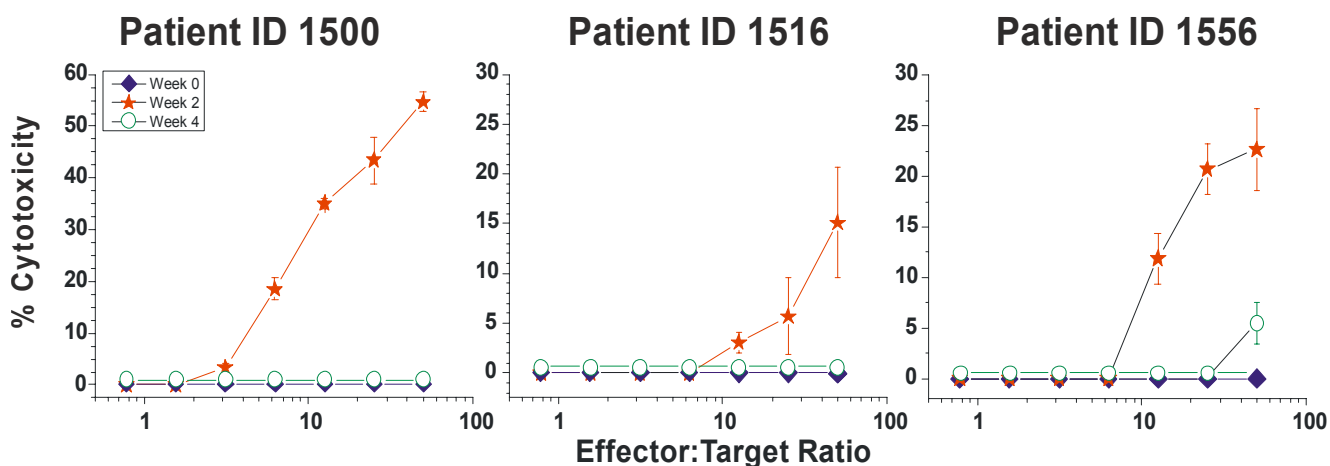
NK cells during culture was seen at Weeks 2 and 4. For the remaining patient, the Week 2 treatment contained activated NK cells both prior to and after culture.

Figure 37 NK Cell Activation during Ex Vivo Culture at Treatment Weeks 0, 2 and 4 (n = 3)



NK lytic activity is measured in vitro using the K562 tumor cell line, which does not express surface MHC I. Figure 38 shows NK lytic activity of sipuleucel-T for all 3 treatments for each of 3 patients. These results show that cells from the Week 2 treatments possessed NK lytic activity as gauged by lysis of the K562 tumor cell line.

Figure 38 NK Lytic Activity at Treatment Weeks 0, 2 and 4 (n = 3)



APPENDIX 3 CLINICAL PHARMACOLOGY STUDIES

Summary of Clinical Studies

Studies with sipuleucel-T have employed measurements of both humoral and cellular responses. T cell responses were assessed by ³H-thymidine incorporation and measured using standard proliferation assays in which antigen (PA2024, PAP, or GM-CSF) was added to cultures of PBMCs. Humoral responses were assessed by ELISA. In the single-arm uncontrolled studies, patients were used as their own controls; positive responses were identified by an increase in the reciprocal antibody titer or T cell proliferation stimulation index (SI) relative to baseline. Stimulation index was defined as the ratio of proliferation in the presence of antigen to the proliferation in the absence of antigen. In a limited number of patients in a later, ongoing randomized trial, Study P-11, the IFN γ enzyme-linked immunospot (ELISPOT) technique was also used. Table 27 displays a list of the clinical pharmacology studies of sipuleucel-T.

Table 27 Tabular Summary of Clinical Pharmacology Studies

Study (status)	Population	Study Phase; Treatment	Analyses
ACT 9610 (complete)	Advanced AIPC	Phase I (N = 12); sipuleucel-T: Weeks 0, 4, 8, and 24 Phase II (N = 19); sipuleucel-T: Weeks 0, 4, 8, and 24	Proliferation; ELISA
ACT 9702 (complete)	Advanced AIPC	Phase I (N = 13); sipuleucel-T: Weeks 0, 4 and PA2024: Weeks 8, 12, 16 Phase II (N = 21); sipuleucel-T: Weeks 0, 2 and PA2024: Weeks 4, 8, 12	Proliferation; ELISA
Study 1 (complete)	Asymptomatic, metastatic, AIPC	Phase III (N = 49); sipuleucel-T or placebo: Weeks 0, 2, and 4	Proliferation; ELISA
P-11 (ongoing)	Non-metastatic ADPC in patients with a rising PSA following radical prostatectomy	Phase III (N = 22); sipuleucel-T or placebo: Weeks 0, 2, and 4, and booster at disease progression	Proliferation; ELISPOT

Abbreviations: ADPC = androgen dependent prostate cancer; AIPC = androgen independent prostate cancer; ELISA = enzyme-linked immunosorbent assay; ELISPOT = enzyme-linked immunospot assay; PSA = prostate specific antigen

Phase III Clinical Pharmacology Studies

T cell Proliferation Results from Study 1

Assessments for cellular and humoral immune responses were performed as exploratory analyses in a subset of patients (n = 49). There was a strong T cell response to PA2024 in patients treated with sipuleucel-T compared to patients treated with placebo (as shown by mean SI in Figure 39 and by median SI ratio in Table 28). These data suggest a robust T cell response to sipuleucel-T and a relatively low baseline response in the placebo group (Week 0 to Week 8 of 16.91 versus 1.99; $P = 0.0004$). The proliferative response was predominantly directed against the PA2024 antigen, with only minimal reactivity directed against the subcomponents (PAP or GM-CSF; Table 28). Whether this represents an absence of PAP specific T cells, issues with the timing of sampling or the tissue compartment being assessed, or methodological issues with the assay is unclear. These are issues that Dendreon, and the field of immunotherapy in general, continue to investigate.

Figure 39 Stimulation Index of PA2024 (50 µg/mL) Over Time, by Treatment Group, Study 1

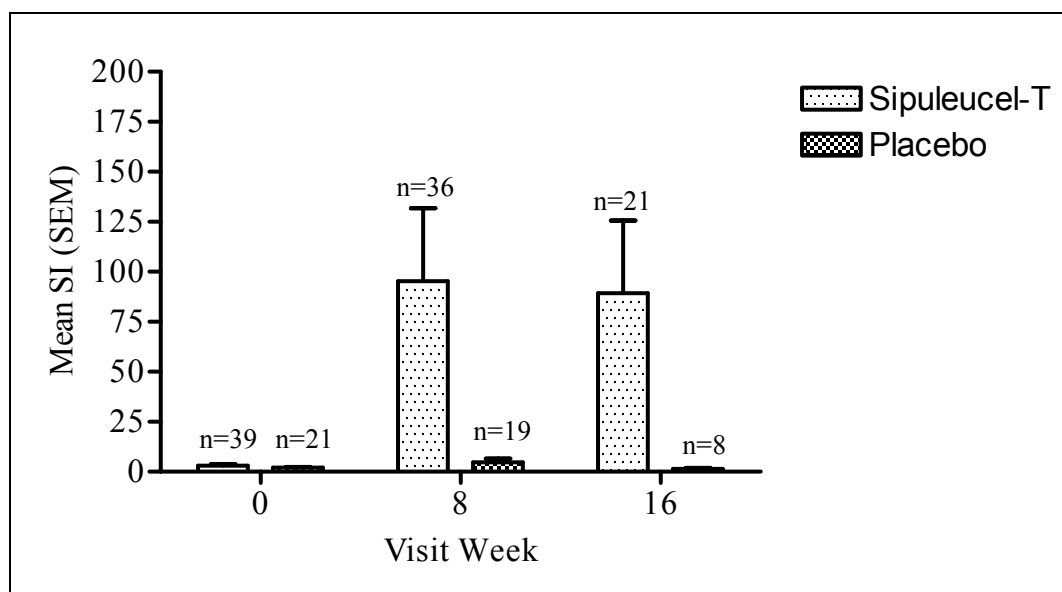


Table 28 Analyses of Stimulation Index Ratios Using Geometric Means and 50 µg/mL of Antigen, Week 0 to Weeks 8 and 16, Study 1

Antigen	Sipuleucel-T	Placebo	p-value ^a
	Median of the Geometric Mean		
Week 0 to Week 8	N=31	N=16	
PA2024	16.91	1.99	0.0004
PAP ^b	1.07	1.90	0.2238
GM-CSF	1.31	1.09	0.7306
Week 0 to Week 16	N=14	N=8	
PA2024	13.22	0.91	0.0001
PAP ^{b,c}	0.99	0.40	0.0890
GM-CSF	0.76	0.37	0.3650

^a p-value compares treatment groups using exact 2-tailed p-value for the Wilcoxon rank sum test.

^b Obtained commercially; purified from human seminal fluid.

^c For sipuleucel-T, N=13

Antibody Response Results from Study 1

Post-treatment antibody responses for all evaluated patients are summarized in [Table 29](#). For the PA2024 antigen, 27 of 30 patients (90.0%) treated with sipuleucel-T experienced a ≥ 16 -fold increase in antibody titer at 1 or more time points following treatment compared to 1 of 17 patients (5.9%) treated with placebo. For human PAP and GM-CSF, 2 of 30 patients (6.9%) treated with sipuleucel-T and 14 of 30 patients (46.7%) treated with sipuleucel-T, respectively, had ≥ 16 -fold increases in antibody titer relative to baseline. No patients treated with placebo experienced an increase in antibody titer to human PAP or GM-CSF relative to baseline.

Table 29 Summary of Antibody Response Data in Study 1^a

	Sipuleucel-T N=30	Placebo N=17
	≥ 16-fold increase in antibody titer	≥ 16-fold increase in antibody titer
PA2024	27 (90.0)	1 (5.9)
Human PAP^b	2 (6.9)	0 (0.0)
GM-CSF	14 (46.7)	0 (0.0)

^aResponse data were not obtained for all patients. The cut-off value for PA2024, human PAP, and GM-CSF is 80. A minimum value of 10 was used for Week 0 antibody titer values that were 0 in order to facilitate a response definition. A positive fold increase could occur at any visit after baseline.

^bObtained commercially; purified from human seminal fluid.

Study P-11

Background: Study P-11 is a randomized, multicenter, double blind, placebo-controlled trial investigating the safety and efficacy of sipuleucel-T in men with androgen dependent prostate cancer. Patients qualifying for this study were men who had previously undergone a prostatectomy and whose only sign of disease recurrence was a rise in serum PSA.

During the treatment and observation period, patients underwent 3 leukapheresis procedures on alternate weeks (Weeks 0, 2, and 4). Approximately 2 days following each leukapheresis procedure, patients received an infusion of either sipuleucel-T or placebo. Patients were evaluated periodically for safety and efficacy endpoints during this period. The endpoint for the treatment and observation period was biochemical failure, specifically the time at which the patient's PSA rose to ≥ 3 ng/mL. Patients were eligible for a booster infusion at the time biochemical failure was confirmed. The booster process consisted of 1 leukapheresis procedure followed approximately 2 days later by 1 infusion of the same treatment assigned at initial randomization (i.e., sipuleucel-T or placebo).

An immunology analysis was conducted according to a sub-study protocol. The immunology analysis used IFN γ ELISPOT and proliferation assays to characterize the immune response

induced by sipuleucel-T. Patients had peripheral blood drawn during regularly scheduled treatment and observation phase appointments at Baseline, Week 4, and Week 13. Following a protocol amendment, a portion of patients also had additional blood drawn at the booster infusion visit (prior to study product infusion) and at visits scheduled 4 and 13 weeks following the booster infusion.

T cell Response: Table 30 presents the immune response to PA2024 by both proliferation and IFN γ ELISPOT, comparing patients who received sipuleucel-T to those who received placebo. For both of these assays, the PA2024 antigen concentration was 10 μ g/mL. The analysis compares the change in response from Week -1 to Week 4 or Week 13. The control-adjusted number of ELISPOTs was first calculated at each time point by subtracting the geometric mean of the number of background spots (no antigen) from the geometric mean of the number of spots in antigen-containing samples. The change from Baseline was determined by subtracting the control-adjusted Baseline (Week -1) value from the corresponding control-adjusted Week 4 or Week 13 value. Only those patients with matched Week -1 and Week 4 and/or Week 13 samples were included in the analysis.

T cell proliferation from patients treated with sipuleucel-T demonstrated a median SI ratio of 28.5, compared to a median stimulation ratio of 0.7 in patients treated with placebo for the Week 4 to Week -1 comparison ($P = 0.00032$, Wilcoxon rank sum test). Similarly, between Week -1 and Week 13, patients treated with sipuleucel-T demonstrated a median stimulation ratio of 38.4 compared to a median SI ratio of 0.9 in patients treated with placebo ($P = 0.00065$, Wilcoxon rank sum test).

When the immune response was measured using the IFN γ ELISPOT assay, a similar treatment effect was observed. The PA2024-specific median change from Week -1 to Week 4 was 63.9 background adjusted spots per 3×10^5 PBMCs for patients treated with sipuleucel-T, compared to 0 spots for patients treated with placebo ($P = 0.00001$, Wilcoxon rank sum test). The results for the response at Week 13 compared to Week -1 were similar: patients treated with sipuleucel-T had a median of 39.7 spots per 3×10^5 PBMCs, while patients treated with placebo had 0.0 spots per 3×10^5 PBMCs ($P = 0.00021$, Wilcoxon rank sum test). Although the number of

evaluated samples was not large, 2 different assays detected a significant difference in the cellular immune response in the patients treated with sipuleucel-T compared to the patients treated with placebo.

Table 30 Study P-11: PA2024 Specific (10 µg/mL) Stimulation Index Ratios of Treatment with Sipuleucel-T Compared to Treatment with Placebo

Assay	Time Comparison from Baseline	Sipuleucel-T		Placebo		p-value ^b
		N	Median ^a	N	Median ^a	
Proliferation ^c	Week -1 to Week 4	12	28.5	5	0.7	0.00032
	Week -1 to Week 13	12	38.4	5	0.9	0.00065
ELISPOT ^d	Week -1 to Week 4	15	63.9	7	0.0	0.00001
	Week -1 to Week 13	14	39.7	6	0.0	0.00021

^a For proliferation: median stimulation index ratio; for ELISPOT: median number of spots per 3×10^5 PBMCs minus background

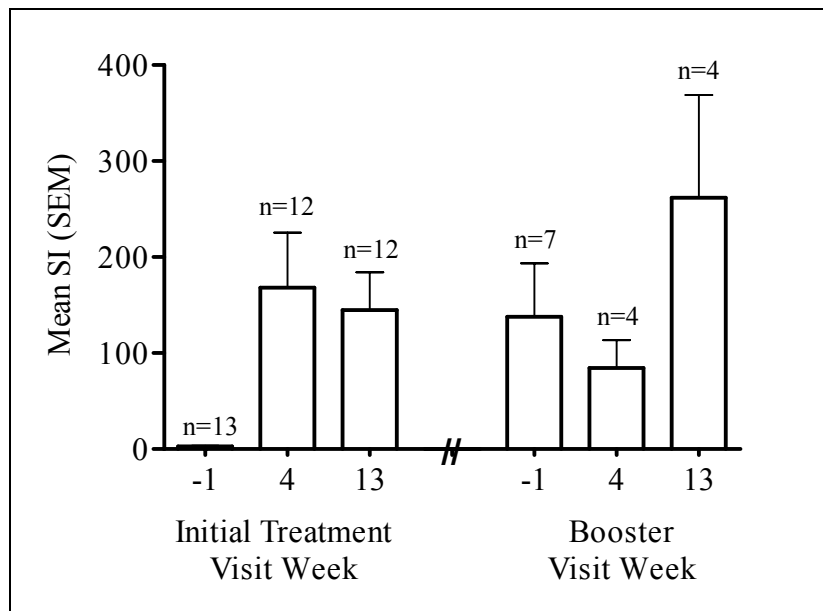
^b p-value calculated using exact method of Wilcoxon rank sum test

^c Change calculated as a ratio of stimulation index Week 4/Week -1 or Week 13/Week -1)

^d Change calculated by subtracting geometric means (Week 4-Week -1 or Week 13-Week -1). Negative numbers are reported as 0.0

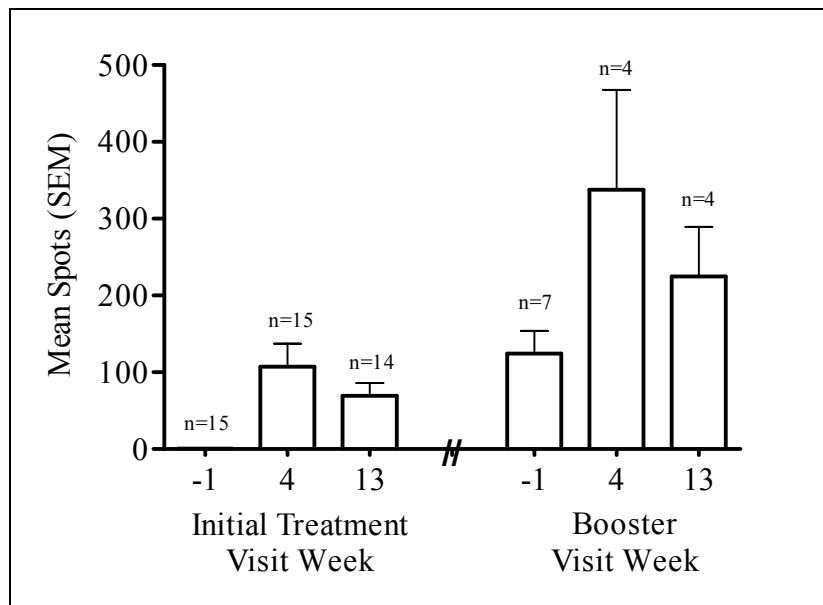
Once their PSA rose to ≥ 3 ng/mL, P-11 patients were eligible for a booster infusion of the same treatment assigned at initial randomization (i.e., sipuleucel-T or placebo). Blood samples were drawn for a small number of patients prior to and after the booster in order to evaluate the durability of the immune response and the ability of the booster to enhance the response at a later time point. [Figure 40](#) shows the PA2024-specific (10 µg/mL) proliferative response for all patients treated with sipuleucel-T who had at least a pre-treatment and post-treatment sample. The time from randomization to the booster ranged from approximately 18 weeks to 140 weeks.

Figure 40 Stimulation Index of PA2024 (10 µg/mL) Over Time for Patients treated with Sipuleucel-T in Study P-11



The ELISPOT data in [Figure 41](#) show a similar trend to that seen for proliferation. The PA2024-specific response (10 µg/mL) measured after more than a year is of similar magnitude to the response at Week 4 or 13. Preliminary results indicate that the response may also be enhanced by a booster infusion.

Figure 41 IFN γ ELISPOT of PA2024 (10 μ g/mL) Over Time for Patients Treated with Sipuleucel-T in Study P-11



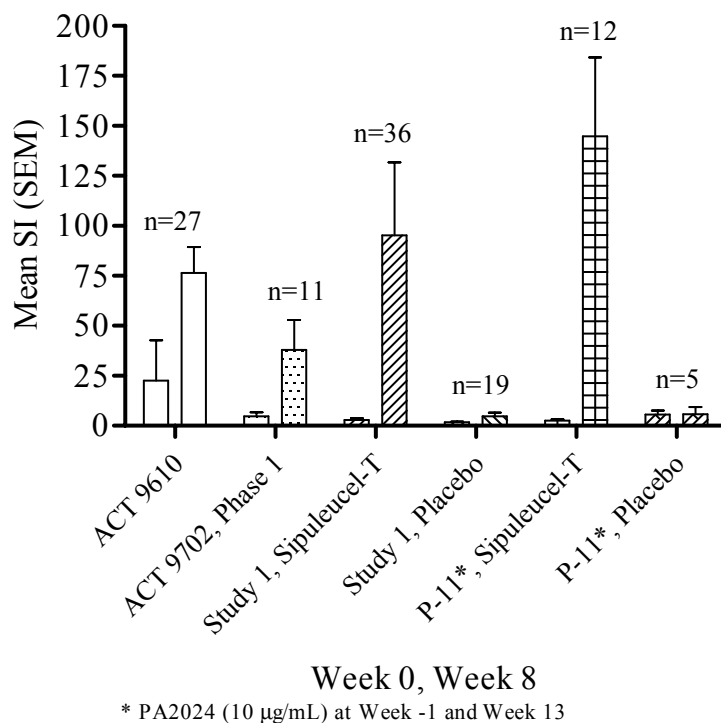
Comparison and Analyses across Trials

T cell Response

The proliferative assay used to measure the PA2024-specific immune response has been utilized throughout clinical development, providing a biological evaluation of T cell response over time.

Figure 42 shows the mean SI at Week 0 and Week 8 for trials of sipuleucel-T to date. T cell responses are fairly consistent from trial to trial, considering the inherent assay and patient variability, and the low number of samples in some of the trials. Placebo responses to PA2024 were markedly lower than the responses to patients treated with sipuleucel-T.

Figure 42 Stimulation Index of PA2024 (50 µg/mL) at Week 0 and Week 8 across All Studies



Antibody Response

Table 31 shows the comparison of antibody responses among Studies ACT 9610, ACT 9702, and Study 1. Data are presented as a ≥ 16 -fold increase in antibody titer at 1 or more time points following treatment. As seen with the T cell responses in Figure 42, robust antibody responses to PA2024 were seen in all studies. The lack of response in the placebo group further underscores the specificity of this immune assay.

Table 31 N (%) of a \geq 16-fold Antibody Response Following Treatment, by Study

Antigen	ACT 9610	ACT 9702	Study 1 (Sipuleucel-T)	Study 1 (Placebo)
PA2024	20 (67)	25 (86)	27 (90)	1 (6)
Seminal PAP	9 (30)	2 (7)	2 (7)	0 (0)
GM-CSF	14 (48)	18 (62)	14 (47)	0 (0)

Clinical Pharmacology Conclusions

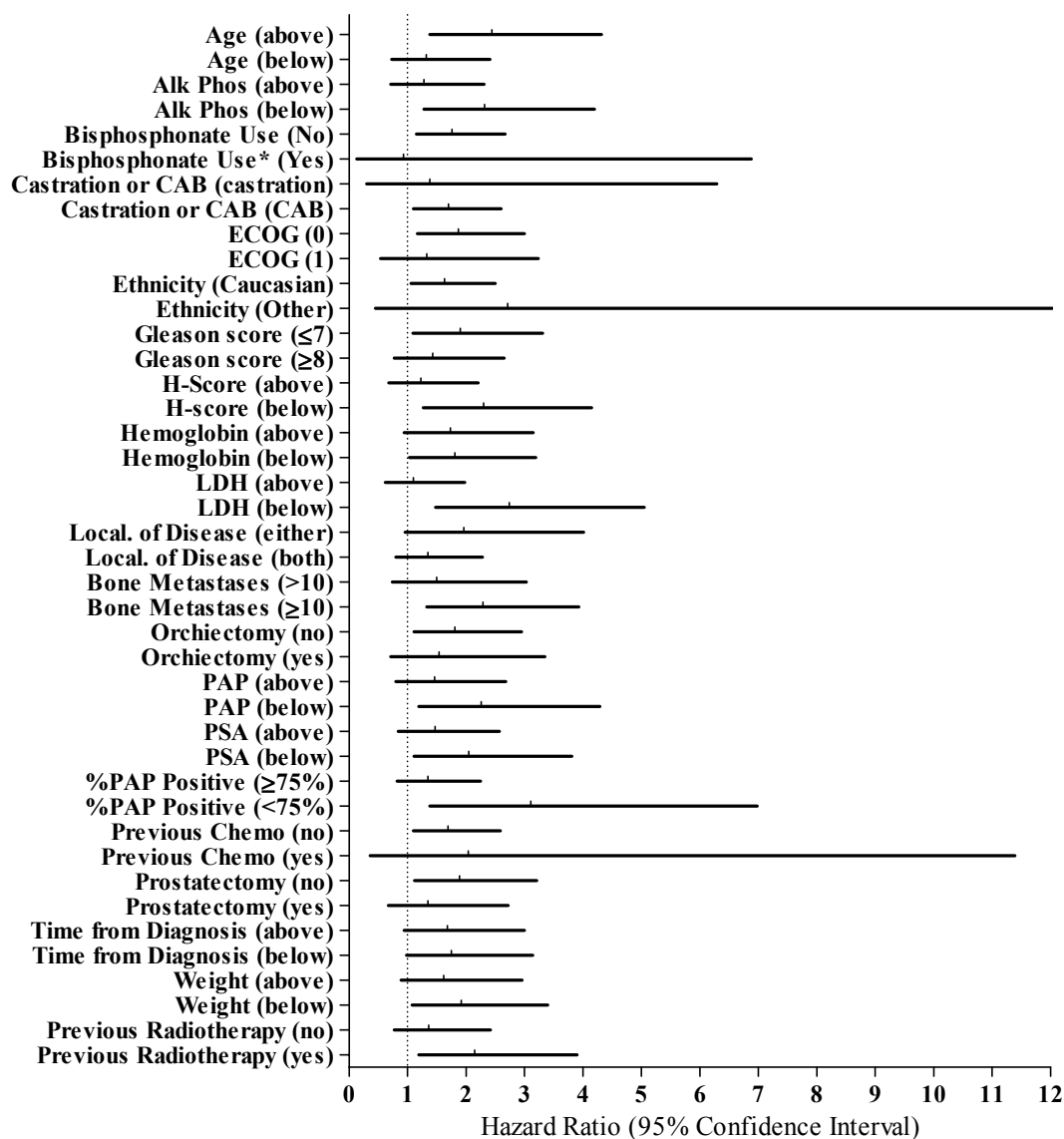
The pharmacodynamic evaluation of sipuleucel-T in men with AIPC participating in Phase I, Phase II, and Phase III trials has focused on the cellular and humoral immune response to the target antigen, PA2024. The data demonstrate that men who receive sipuleucel-T mount a significant immune response against PA2024. Early studies of dosing regimens and routes of administration helped define the dose for the Phase III studies. Immune monitoring data from Phase III studies were exploratory, but did demonstrate the in vivo activity of sipuleucel-T.

APPENDIX 4 REFERENCES FOR SIGNIFICANT PROGNOSTIC FACTORS OF SURVIVAL IN COX MULTIPLE REGRESSION MODELS

Covariate	Reference
Age	(Scher, 1999) (DeWys, 1983) (Wyatt, 2004)
Hemoglobin	(Emrich, 1985) (Fossa, 1992) (Scher, 1999) (Vollmer, 1999) (Smaletz, 2002) (Halabi, 2003)
LDH	(Petrylak, 1992) (Kelly, 1993) (Scher, 1999) (Smaletz, 2002) (Halabi, 2003) ^a (Small, 2002) ^a
Alkaline Phosphatase	(Emrich, 1985) (Petrylak, 1992) (Smaletz, 2002) (Halabi, 2003) ^a
PSA	(Fossa, 1992) (Kelly, 1993) (Scher, 1999) (Vollmer, 1998) ^a (Vollmer, 1999) ^a (Halabi, 2003) ^a (Dawson, 2000) ^a (DeWys, 1983) ^a (Small, 2002) ^a (Wyatt, 2004) ^a
Body Weight	(Vollmer, 1999) (Dawson, 2000) (DeWys, 1983)
Bone Lesion Count	(Collette, 2004) (Scholz, 2005) (Soloway, 1989) (Akimoto, 1999)
Localization of Disease	(Halabi, 2003) (Dawson, 2000) (DeWys, 1983) (Wyatt, 2004)

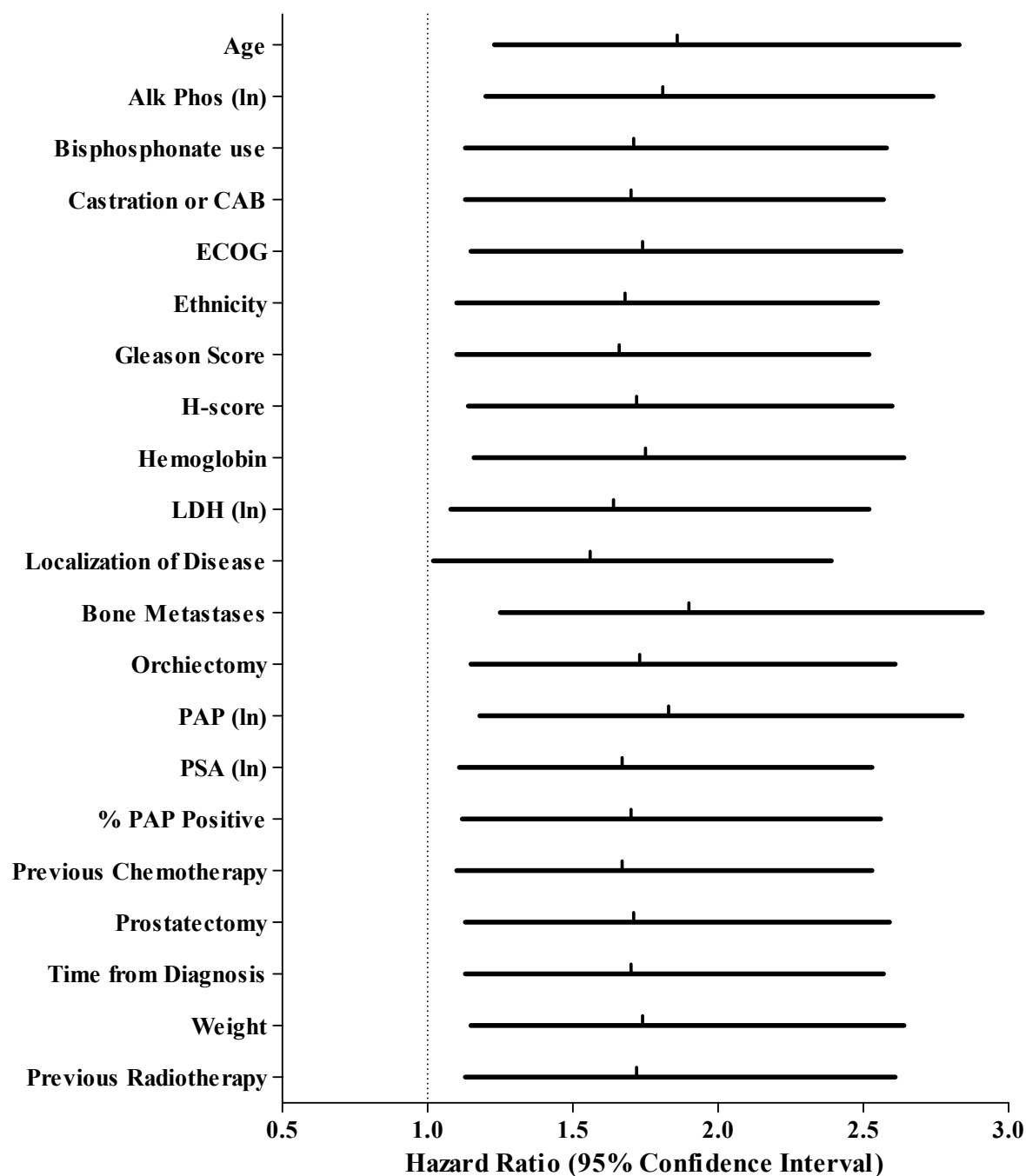
^a Log

APPENDIX 5 SIPULEUCEL-T TREATMENT EFFECT IS CONSISTENT IN STUDY 1 SUB-POPULATIONS BASED ON BASELINE PROGNOSTIC VARIABLES



* N=6

APPENDIX 6 HAZARD RATIO AND 95% CI FOR THE TREATMENT EFFECT ON OVERALL SURVIVAL IN STUDY 1 ADJUSTED FOR EACH POTENTIAL PROGNOSTIC FACTOR INDIVIDUALLY



APPENDIX 7 SUMMARY OF INTEGRATED STUDY 1 AND STUDY 2 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and Baseline Characteristics

Table 32 shows the balance of baseline characteristics and laboratory evaluations between treatment arms in the integrated Studies 1 and 2. The treatment groups were similar with regard to median age, weight, race, performance status, and prior chemotherapy for prostate cancer. The groups were also comparable with regard to a variety of potentially prognostic laboratory values (including median baseline PSA, PAP, alkaline phosphatase, hemoglobin, and LDH). The p-value was > 0.05 for all comparisons of the demographic data.

Table 32 Baseline Characteristics and Laboratory Values, Integrated Studies 1 and 2

Characteristic	Sipuleucel-T (n = 65)	Placebo (n = 33)
Median Age, years (range)	72 (47 – 85)	71 (50 – 87)
Median Weight (pounds)	193.4	186.5
ECOG 0 (%)	76.9	76.9
Ethnicity: Caucasian, (%)	89.8	93.6
Median PSA, ng/mL	50.7	45.8
Median PAP, ng/mL	6.2	6.3
Median alk phos., U/L	114.0	95.5
Median hemoglobin, g/dL	13.0	12.9
Median LDH, U/L	183.0	176.5
Prior Chemotherapy use (% Yes)	6.9	9.0

A greater percentage of patients in the sipuleucel-T arm entered the study with well or moderately differentiated tumors as assessed by Gleason score (64.4% in sipuleucel-T arm versus 53.8% in placebo arm), with bone-only disease (44.5% in sipuleucel-T arm versus 26.7% in placebo arm; [Table 33](#)) and with more than 10 metastatic lesions (45.5% in sipuleucel-T arm versus 31.2% in placebo arm). The p-values for these differences were > 0.05 .

Table 33 Baseline Disease Parameters, Integrated Studies 1 and 2

Characteristic	Sipuleucel-T (n = 147)	Placebo (n = 78)
Gleason score, (%)		
≤ 7	64.4	53.8
> 7	35.6	46.2
Disease Location, (%)		
Bone only	44.5	26.7
Soft tissue only	8.2	13.3
Bone and soft tissue	47.3	60.0
Number of Bone Metastases per patient, (%)		
≤ 10	54.5	68.8
> 10	45.5	31.2