

CLINICAL REVIEW

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Division / Office	Division of Clinical Evaluation and Pharmacology / Toxicology Office of Cellular, Tissue, and Gene Therapy
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Review Completion Date	04/28/2010
Established Name	Sipuleucel-T
(Proposed) Trade Name	Provenge®
Therapeutic Class	Autologous Cellular Immunotherapy
Applicant	Dendreon Corporation
Formulation(s)	Cell suspension in Lactated Ringer's Injection (USP)
Dosing Regimen	Three doses administered via intravenous infusions at two-week intervals
Indication(s)	Treatment of asymptomatic or minimally symptomatic metastatic hormone refractory prostate cancer
Intended Population(s)	Asymptomatic or minimally symptomatic metastatic hormone refractory prostate cancer

Table of Contents

1. RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	6
1.1 Recommendation on Regulatory Action	6
1.2 Risk Benefit Assessment.....	6
1.3 Recommendations for Postmarketing Risk Evaluation and Mitigation.....	9
1.4 Recommendations for Postmarketing Requirements and Commitments.....	9
2. INTRODUCTION AND REGULATORY BACKGROUND	9
2.1 Product Information	9
2.2 Prostate Cancer	10
2.3 Availability of Proposed Active Ingredient in the United States	11
2.4 Important Safety Issues with Related Drugs.....	11
2.5 Presubmission Regulatory Activity	11
2.6 Other Relevant Background Information	14
3 ETHICS AND GOOD CLINICAL PRACTICES.....	14
3.1 Submission Quality and Integrity	14
3.2 Compliance with Good Clinical Practices	15
3.3 Financial Disclosures.....	16
4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	16
4.1 Chemistry Manufacturing and Controls	16
4.2 Preclinical Pharmacology/Toxicology	17
4.3 Statistics	17
4.4 Epidemiology	17
5. SOURCES OF CLINICAL DATA.....	18
5.1 Tables of Studies/Clinical Trials	18
5.2 Review Strategy	19
5.3 Discussion of Individual Studies/Clinical Trials.....	19
5.3.1 Study D9902B	19
5.3.2 Supportive Studies	24
6 REVIEW OF EFFICACY	25
6.1 Efficacy Summary.....	26
6.2 Indication studied	26
6.3 Methods.....	26
6.4 Demographics	26
6.5 Subject Disposition	29
6.6 Analysis of Primary Endpoint(s)	33
6.6.1 Interim analysis	33
6.6.2 Primary analysis	33
6.6.3 Subgroup Analyses	35
6.6.4 Sensitivity Analyses:.....	38

6.6.5	APC8015F Sensitivity Analysis	39
6.6.6	Docetaxel Sensitivity Analyses	41
6.6.7	Analysis of Secondary Endpoint(s)	45
6.6.8	Analysis of Tertiary Endpoints	46
6.6.9	Analysis of Other Endpoints	47
6.6.10	Analysis of Subpopulations:	47
6.6.11	Analysis of Clinical Information Relevant to Dosing Recommendations	48
6.6.12	Additional Efficacy Issues and Analyses	48
7	REVIEW OF SAFETY	49
7.1	Safety Summary	49
7.2	Methods	50
7.2.1	Studies/Clinical Trials Used to Evaluate Safety	51
7.2.2	Categorization of Adverse Events	51
7.2.3	Pooling of Data Across Studies/Clinical Trials	52
7.2.4	Adequacy of Safety Assessments	52
7.2.5	Overall Exposure at Appropriate Doses/Durations	54
7.2.6	Demographics of Target Populations	54
7.2.7	Explorations for Dose Response	56
7.2.8	Special Animal and/or In Vitro Testing	57
7.2.9	Routine Clinical Testing	57
7.2.10	Metabolic, Clearance, and Interaction Workup	57
7.2.11	Evaluation for Potential Adverse Events for Similar Drug Classes	57
7.3	Major Safety Results	57
7.3.1	Deaths	57
7.3.2	Nonfatal Serious Adverse Events	62
7.3.3	Dropouts and/or Discontinuations	65
7.3.4	Significant Adverse Events	65
7.3.5	Submission Specific Primary Safety Concerns	67
7.4	Supportive Safety Results	77
7.4.1	Common Adverse Events	77
7.4.2	Laboratory Findings	84
7.4.3	Vital Signs	85
7.4.4	Electrocardiograms (ECGs)	85
7.4.5	Special Safety Studies/Clinical Trials	85
7.4.6	Immunogenicity	85
7.5	Other Safety Explorations	85
7.5.1	Dose Dependency for Adverse Events	85
7.5.2	Time Dependency for Adverse Events	86
7.5.3	Drug-Demographic Interactions	86
7.5.4	Drug-Disease Interactions	87
7.5.5	Drug-Drug Interactions	87
7.6	Additional Safety Evaluations	88
7.6.1	Human Carcinogenicity	88
7.6.2	Human Reproduction and Pregnancy Data	88
7.6.3	Pediatrics and Assessment of Effects on Growth	88
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound	88

7.7	Additional Submissions / Safety Issues	88
8	POSTMARKET EXPERIENCE.....	89
9	APPENDICES	89
A.	Advisory Committee Meeting.....	89
B.	Labeling Recommendations.....	89
C.	Protocol and Amendments to the Protocol.....	90
D.	Review of Major Protocol Deviations.....	109
E.	Narratives of Death Associated with CVE's.....	113
F.	Narratives of Cases Associated with Acute Cardiac Arrhythmias.....	115
G.	Literature Review/References.....	116

Table of Tables

Table 1:	Summary of Overall Survival results, three randomized studies	8
Table 2:	Available therapies for metastatic prostate cancer	10
Table 3:	Survival Efficacy Analysis for Docetaxel in TAX 327	11
Table 4:	Summary of Relevant Regulatory Milestones.....	11
Table 5:	Summary of BLA amendments.....	14
Table 6:	CBER Bioresearch Monitoring Branch inspections of D9902B clinical sites	Error! Bookmark not defined.
Table 7:	Summary of Clinical Studies.....	18
Table 8:	Summary of Demographics and Baseline Characteristics.....	27
Table 9:	Summary of Baseline Laboratory Values, Intent-to-Treat Population.....	28
Table 10:	Predicted Survival by Treatment based on Halabi Scores	28
Table 11:	Summary of Baseline Stratification Factors, ITT Population *	29
Table 12:	Major Protocol Deviations.....	32
Table 13:	Primary Analysis of Overall Survival.....	34
Table 14:	FDA Statistical Reviewer's Analysis of Survival in Subjects < 65 years old ..	38
Table 15:	Summary of first non-study anti-cancer interventions.....	41
Table 16:	FDA analyses of the Effect of Timing of Docetaxel therapy	43
Table 17:	Summary of Time to Objective Disease Progression (ITT Population).....	45
Table 18:	Demographic and Baseline Characteristics, Safety Database	54
Table 19:	Summary of leukaphereses and infusion(s), safety population	55
Table 20:	Cumulative Cell Product Parameters Administered in Safety Database	56
Table 21:	Summary of Deaths in the Safety Database.....	58
Table 22:	Summary of Causes of Deaths in the Safety Database	59
Table 23:	Summary of "Other and Unknown" Causes of Deaths, Safety Database	59
Table 24:	Time from Initial Product Infusion to Death, Safety Database	60
Table 25:	Summary of SAEs, by Preferred Term and Treatment group.....	62
Table 26:	Incidence of Serious Adverse Events by System Organ Class	64
Table 27:	Incidence of Adverse Events by Toxicity Grade	66
Table 28:	Incidence of Grade 3 -5 AEs in ≥ 1% of Subjects.....	67
Table 29:	Summary of Incidence and Characteristics of Cerebrovascular Events	68

Table 30: Summary of Risk Factors of Cerebrovascular Events	69
Table 31: Summary of Etiology of CVE-Associated Deaths*	70
Table 32: Incidence of Non-Neurologic Arterial Events	71
Table 33: Incidence of Non-Neurologic Venous Events	71
Table 34 : Respiratory Adverse Events following Product Infusion	75
Table 35: Summary of AEs \geq 5% Safety population.....	77
Table 36: Summary of AEs Occurring \leq 1 Day Following a Leukapheresis Procedure .	79
Table 37: Summary of AEs Occurring \leq 1 Day Following Infusion	80
Table 38: AEs Occurring in \leq 14 days Following Infusion of the Study Product	81
Table 39: Incidences of NCI CTCAE Acute Infusion Reaction AEs.....	82
Table 40: Grade 3 Acute Infusion Reaction Occurring \leq 1 Day Following Infusion	83
Table 41: Summary of Hospitalizations for Acute Infusion Reactions	83
Table 42: FDA review of individual death data	112

Table of Figures

Figure 1: Study D9902B Overall Schema.....	20
Figure 2: Kaplan-Meier Analysis of Overall Survival (ITT Population).....	35
Figure 3: Applicant's Analyses of Subgroups Based on Baseline Covariates.	36
Figure 4: Applicant's Additional Analyses of Subgroup Survival Consistency	37
Figure 5: Applicant's Analysis of effects of APC8015F on overall survival	40
Figure 6: Applicant's survival sensitivity analysis for docetaxel effect	42
Figure 7: FDA Statistical Reviewer's Sensitivity Analysis by Docetaxel Subgroup.....	44
Figure 8: Kaplan-Meier Time to Objective Disease Progression in ITT population	45

1. Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The reviewers recommend approval of sipuleucel-T (Provenge®) administered in three intravenous doses at 2-week intervals for the treatment of asymptomatic or minimally symptomatic, metastatic, castrate resistant (hormone refractory) prostate cancer.

1.2 Risk Benefit Assessment

The risk benefit analysis to support this recommendation is based on efficacy results from three similar, double-blind, placebo-controlled, multi-center Phase 3 studies (D9901, D9902A and D9902B) that randomized in a 2:1 ratio of sipuleucel-T to control a total of 737 subjects with asymptomatic or minimally symptomatic metastatic AIPC. Safety information was derived from 904 patients randomized to sipuleucel-T or control in four randomized trials: D9901, D9902A, D9902B, and P-11.

Sipuleucel-T consists of autologous peripheral blood mononuclear cells, including antigen presenting cells, that have been activated during a defined culture period with a recombinant fusion protein consisting of prostatic acid phosphatase (PAP), an antigen expressed in prostate cancer tissue, linked to granulocyte-macrophage colony-stimulating factor (GM-CSF), an immune cell activator. The patient's peripheral blood mononuclear cells are obtained via a standard leukapheresis procedure approximately 3 days prior to the infusion date. The course of therapy consisted of 3 doses of sipuleucel-T, given at approximately 2-week intervals, each dose containing a minimum of 50 million autologous CD54⁺ cells activated with PAP-GM-CSF. The control group was given the same dosing regimen of autologous peripheral blood mononuclear cells that had not been activated. Following disease progression, all patients had the option of receiving additional cancer therapy; control group patients could choose to receive autologous frozen, thawed, and PAP-GM-CSF activated mononuclear cells.

Study D9901 was a randomized, double-blind, placebo-controlled, multi-center trial in patients with asymptomatic metastatic castrate resistant prostate cancer. A total of 127 subjects were randomized in a 2:1 ratio to receive sipuleucel-T (n = 82) or placebo (n = 45). The primary endpoint was time to disease progression (TTP). Study treatment included leukapheresis followed by intravenous infusions of sipuleucel-T or placebo (autologous PBMC's not loaded with PA2024 antigen) given on Weeks 0, 2, and 4. Upon progression, subjects could be unblinded to study treatment and receive 'salvage' chemotherapy. Subjects in the placebo arm were provided the option of receiving APC 8015F (cryopreserved APC from the initial leukapheresis, thawed and loaded with PA2024 antigen) administered via the same route and schedule as sipuleucel-T. All subjects were followed for survival; however, the method for survival analysis was not pre-specified. The primary objective of demonstrating an improvement in TTP was not achieved; however, a subsequent analysis of the survival results of D9901 showed a 4.5 month difference in survival favoring the sipuleucel-T arm (median 25.9 vs. 21.4 months). Since the applicant had not pre-specified a method for survival analysis, and the primary objective was not achieved, the log rank p-value of 0.01 was difficult to interpret.

BLA 125197, Sipuleucel-T CBER Clinical Review

Study D9902A was similar in design to D9901 and randomized ninety-eight subjects to receive sipuleucel-T (n=65) or placebo (n=33) but was closed prior to completion of accrual. Study D9902A showed a similar trend in survival but was terminated prematurely and efficacy results were inconclusive. Exploratory sensitivity analyses showed consistent effects among subgroups; however, there was no benefit observed on time to objective disease progression, time to clinical progression, PSA progression, or pain.

A BLA submission was filed in 2006 based on the survival difference observed in D9901. The BLA submission was reviewed by FDA and the application was discussed at the FDA Cell Tissue and Gene Therapy Advisory Committee on March 29 2007 and received a positive recommendation for licensure. However, due to the small population studied and lack of statistical persuasiveness of the submitted information, the FDA issued a complete response letter requiring submission of survival results of the third randomized study, D9902B, prior to making a licensure decision.

Study D9902B was a 2:1 randomized, placebo-controlled, double-blind, multi-center, phase 3 study in patients with asymptomatic or minimally symptomatic, metastatic, castrate resistant (hormone refractory) prostate cancer. Subjects were randomized based on three stratification variables: primary gleason grade, number of bone metastases and bisphosphonate use. Treatment regimen was the same as those administered in the previous studies D9901 and D9902A. Subjects could be unblinded following progression and receive either chemotherapy or APC 8015F if they were on the control arm as in the previous studies. The initial co-primary efficacy endpoints were time to radiological progression and development of disease related pain; patients with cancer related pain were excluded. After analysis of survival results of D9901 the primary objective of D9902B was changed to overall survival measured from the date of randomization in the intent-to-treat population. Patients with mild cancer related symptoms were allowed to enroll. FDA agreed to this change under a Special Protocol Assessment.

Study D9902B enrolled 512 subjects: 341 subject in the sipuleucel-T arm and 171 subjects in the placebo arm. The two arms were fairly balanced for baseline characteristics, prior therapies for prostate cancer, predicted survival based on the Halabi prognostic score, and the three stratification factors. An interim analysis did not meet stopping criteria. The primary analysis of overall survival in Study D9902B was conducted when a total of 331 death events had occurred (210 death events in the sipuleucel-T arm and 121 death events in the placebo arm) with median follow-up period of 33.7 months for the sipuleucel-T arm and 35.9 months for the placebo arm. The primary analysis showed a statistically significant difference in overall survival favoring the sipuleucel-T arm (p-value of 0.032), with HR of death of 0.0775 (95% CI 0.614, 0.979). The difference in median survival times was 4.1 months (25.8 months vs. 21.7 months) in favor of sipuleucel-T.

Fifty-seven percent of subjects in the sipuleucel-T arm and 50.3% of subjects in the placebo arm received treatment with docetaxel after disease progression. Sensitivity analyses were performed to explore the interaction of subsequent docetaxel therapy. However, due to the likelihood of selection bias, this analysis did not yield any conclusions or any hypothesis regarding the interaction of subsequent docetaxel on overall survival. It is not possible to determine the precise effect of subsequent therapy with docetaxel on survival.

Efficacy results of the three randomized studies in patients with asymptomatic or minimally symptomatic, metastatic, androgen independent prostate adenocarcinoma are summarized in Table 1 below:

Table 1: Summary of Overall Survival results, three randomized studies

	Study D9902B		Study D9901		Study D9902A	
Overall Survival	Sipuleucel-T [®] (N=341)	Placebo (N=171)	Sipuleucel-T [®] (N=82)	Placebo (N=45)	Sipuleucel-T [®] (N=65)	Placebo (N=33)
Median, months (95% CI)	25.8 (22.8, 27.7)	21.7 (17.7, 23.8)	25.9 (20.0, 32.4)	21.4 (12.3, 25.8)	19.0 (13.6, 31.9)	15.7 (12.8, 25.4)
Hazard Ratio (95% CI)	0.775 (0.614, 0.979)		0.586 (0.388, 0.884)		0.786 (0.484, 1.278)	
p-value	0.032 ^a		0.010 ^b		0.331 ^b	
^a Test statistic based on the Cox Model adjusted for PSA (ln) and LDH (ln) and stratified by bisphosphonate use, number of bone metastases, and primary Gleason grade. ^b Hazard ratio based on the unadjusted Cox Model and p-values based on an un-prespecified test (log-rank). Abbreviations: CI = confidence interval.						

Safety: The safety of sipuleucel-T was evaluated in 904 patients randomized 2:1 in four blinded, placebo-controlled studies (D9901, D9902A, D9902B, and P11). The study design and patient population, metastatic androgen independent prostate cancer, were similar in Studies D9901, D9902A, and D9902B; study P11 enrolled patients with androgen sensitive prostate cancer. The treatments were identical and the safety profile of Study P11 appeared similar to that of the other studies. Therefore safety data from the four randomized studies was pooled to allow for a larger safety database. A total of 904 subjects who underwent at least 1 leukapheresis were included in the safety analysis population, 601 in the sipuleucel-T group and 303 in the placebo group.

Deaths: Disease progression was the most common cause of death in the safety analysis population, including 240/320 (75%) of deaths that occurred in the sipuleucel-T group and 151/187 (80%) of deaths in the placebo group prior to data cutoff. A higher percentage of patient deaths were attributed to disease progression in the placebo group than in the sipuleucel-T group.

Acute infusion reactions: Following infusion, 71% of patients in the sipuleucel-T group developed an acute infusion reaction compared with 29% of patients in the control group. Acute infusion reactions (occurring within one day of infusion) included pyrexia (fever), chills, respiratory events (dyspnea, hypoxia, and bronchospasm), nausea, vomiting, fatigue, hypertension, and tachycardia. The most common events (occurring in $\geq 20\%$ of patients) were chills, pyrexia (fever), and fatigue. The majority of events were mild or moderate.

Serious adverse events: Overall serious adverse events were balanced between groups. There was a slightly higher incidence of CVEs observed in the sipuleucel-T group compared with the control group, 24 (4.0%) versus 9 (2.9%).

Common events: The most common adverse events observed in $\geq 15\%$ of sipuleucel-T-treated patients were chills, fatigue, pyrexia (fever), back pain, nausea, arthralgia, and headache. The majority (67%) of adverse events were mild or moderate in severity.

Safety of Leukapheresis: Each dose of sipuleucel-T is preceded by a leukapheresis procedure approximately 2 to 3 days prior to the infusion. Adverse events that occurred ≤ 1 day following a leukapheresis in $\geq 5\%$ of patients in controlled clinical trials included citrate toxicity (14.2%), paresthesia (11.4%), and fatigue (8.3%).

Safety Conclusions: Overall, sipuleucel-T treatment was relatively well tolerated. 841 (93%) subjects received the scheduled three infusions of either sipuleucel-T or placebo. Most subjects developed adverse events during the study, 98.3% in the sipuleucel-T group and 96.0% in the placebo group. Most (67%) subjects had only mild or moderate adverse events, most of which resolved within 48 hours. Chills, fatigue, pyrexia, back pain, and nausea were the most common AEs ($\geq 20\%$ of subjects in the Sipuleucel-T group). These events generally occurred within one day of an infusion with sipuleucel-T, were grade 1 or 2, and were managed on an outpatient basis. Disease progression was the primary cause of death for both treatment groups. Cerebrovascular events (CVEs) occurred in more subjects in the sipuleucel-T group than in the placebo group: 4.0% versus 2.9% (including transient ischemic attacks (TIA)). However, there were multiple confounding factors which could have contributed to these differences in the incidence of both fatal and total CVEs. The increased CVE frequency associated with sipuleucel-T represents a potential safety concern.

1.3 Recommendations for Postmarketing Risk Evaluation and Mitigation

None at this time.

1.4 Recommendations for Postmarketing Requirements and Commitments

Applicant will be required to conduct a postmarketing study based on a registry design to assess the risk of cerebrovascular events in at least 1,500 patients with prostate cancer who receive sipuleucel-T. See separate review by Office of Biostatistics and Epidemiology.

2. Introduction and Regulatory Background

2.1 Product Information

Sipuleucel-T consists of autologous peripheral blood mononuclear cells, including antigen presenting cells, that have been activated during a defined culture period with a recombinant fusion protein consisting of prostatic acid phosphatase (PAP), an antigen expressed in prostate cancer tissue, linked to granulocyte-macrophage colony-stimulating factor (GM-CSF), an immune cell activator. The patient's peripheral blood mononuclear cells are obtained via a standard leukapheresis procedure approximately 3 days prior to the infusion date. The active components are autologous antigen presenting cells and human PAP-GM-CSF fusion protein. During culture, the recombinant antigen can bind to and be processed by antigen presenting cells into smaller protein fragments. The recombinant antigen is

designed to target antigen presenting cells, and may help direct the immune response to PAP. Minimal residual levels of the intact human PAP-GM-CSF fusion protein are detectable in the final sipuleucel-T product. The cellular composition of sipuleucel-T is dependent on the composition of cells obtained from the patient's leukapheresis. Each dose contains a minimum of 50×10^6 CD54⁺ cells suspended in 250 mL of Lactated Ringer's Injection, USP.

2.2 Prostate Cancer

An estimated 27,360 patients died due to prostate cancer in the US in 2009.¹ An estimated 192,280 new cases of prostate cancer were diagnosed in 2009 in the US. Of these new cases, for subjects who undergo definitive therapy, 20-40% will have disease progression requiring androgen deprivation therapy.² Almost all patients requiring androgen deprivation therapy will have metastases to distant sites, mainly to bone and lymph nodes.^{3,4,5} Prognostic factors that impact overall survival of patients with progressive metastatic prostate cancer after medical or surgical castration include performance status, hemoglobin, alkaline phosphatase, albumin, and LDH.⁶ For subjects with castrate recurrent prostate cancer who do not have metastatic disease, salvage therapy options include enrollment in a clinical trial, observation, androgen withdrawal, and secondary androgen deprivation therapy (ADT). For subjects with castrate recurrent prostate cancer who have metastatic disease, salvage therapy options include docetaxel therapy, secondary ADT, mitoxantrone therapy, palliative therapy with radiation or radionuclide agents for treatment of symptomatic bone disease, and bisphosphonates for prevention of complications due to bone metastases.⁷

Available Treatments for Metastatic Prostate Cancer

Currently available therapies for metastatic prostate cancer are included in Table 2 below.

Table 2: Available therapies for metastatic prostate cancer

Drug	Date of Approval	Class of Drug	Benefit
Estramustine	1981	Estradiol+nor-nitrogen mustard	Palliative pain response
Mitoxantrone	1996	Anthracenedione	Palliative pain response
Zoledronic acid	2002	Bisphosphonate	Decreased skeletal-related events
Docetaxel	2004	Taxoid (mitosis inhibitor)	Improved overall survival

Docetaxel:

Docetaxel was approved in 2004 for use with prednisone in patients with androgen independent (hormone refractory) metastatic prostate cancer.⁸ The approval was based on the results of a Phase 3 randomized controlled study (TAX 327) with 1006 patients randomized to 3 arms with docetaxel given at 75mg/m² given every 3 weeks for 10 cycles vs. docetaxel given at 30 mg/m² given every week for 5

weeks out of 6 weeks and repeated for 5 cycles vs. mitoxantrone at 12mg/m² given every 3 weeks for 10 cycles, with all three regimens given with 5 mg of prednisone twice daily continuously. The primary endpoint was overall survival, and the study results were as follows:

Table 3: Survival Efficacy Analysis for Docetaxel in TAX 327

Analysis	Taxotere (every 3 weeks) (n=335)	Mitoxantrone (every 3 weeks) (n=337)
Median Survival (mo)	18.9; 95% CI (17-21.2)	16.5; 95% CI (14.4-18.6)
Hazard Ratio	0.761; 95% CI (0.619-0.936)	
p-value (threshold significance of 0.0175 due to 3 arms)	0.0094 (stratified log rank test)	

2.3 Availability of Proposed Active Ingredient in the United States

Sipuleucel-T is currently not marketed in the United States or any other country.

2.4 Important Safety Issues with Related Drugs

Sipuleucel-T is a first-in-class biologic. There are no related drugs or biologics on the market, and no known safety issues with related drugs. Theoretical risks of this type of product include product contamination and administration of autologous product to the wrong person. These risks are addressed in the CMC review.

2.5 Presubmission Regulatory Activity

Table 4: Summary of Relevant Regulatory Milestones

Date	Milestone Description	Outcome
22 DEC 1996	IND Original submission, BB-IND 6933, in effect.	Phase 1 trial initiated.
03 NOV 1998	End of Phase 2 Meeting to discuss a prospective Phase 3 trial including product issues, clinical target population, study endpoints, assessment of treatment benefit, and appropriate controls.	FDA provided recommendations regarding the design of the Phase 3 trial efficacy endpoints (including a requirement for survival data submission and concerns about the crossover design), patient population, control arm, and maintenance of blinding. FDA reminded applicant that a single trial with a TTP endpoint would be unlikely to support licensure that additional studies would be likely to be required, and that comparisons of survival between study arms would have to be performed.

BLA 125197, Sipuleucel-T
 CBER Clinical Review

Date	Milestone Description	Outcome
04 MAR 1999	Follow-Up to End of Phase 2 Teleconference to discuss a prospective Phase 3 trial and a Phase 2 open-label salvage trial	FDA provided additional recommendations regarding the design of the Phase 3 (progression endpoints, study procedures, analytical plan). Applicant agreed to capture survival data although the primary endpoint was time to disease progression.
03 SEP 1999	Follow-Up to End of Phase 2 Teleconference on Phase 3 Protocols D9901 and D9902, discussing study design and statistical analysis plan	FDA agreed to the design of Studies D9901 and D9902 (including the efficacy endpoints, patient population, control arm, and study procedures) and the proposed analyses. FDA stated that the original population was insufficient for the safety database, but agreed that a 2:1 ratio of drug to placebo would provide sufficient safety data.
20 JUL 2001	Sipuleucel-T Clinical Development Plan and new Phase 3 study P-11	FDA agreed that the clinical development plan (D9901 and D9902) was sufficient to support a license application for sipuleucel-T; FDA requested clarification of objective disease progression endpoint.
26 JUL 2002	D9901 Final Statistical Analysis Plan (SAP) submitted to FDA	SAP concurrence by FDA.
Oct 2002	D9901 Primary Analysis	Results of Study D9901 analysis demonstrated that overall study results were negative, but sipuleucel-T delayed time to objective disease progression in the ITT population with a statistically significant treatment effect of delaying time to objective disease progression in the non-pre-specified subgroup of patients with Gleason score ≤ 7 . Data submitted to FDA and discussed at the Type A Meeting as noted below.
22 NOV 2002	Type A Meeting to discuss results of D9901 and proposed changes to D9902	Based on the above findings of the D9901 primary analysis, FDA agreed that Study D9902 could be split into two parts: D9902A would include subjects already enrolled regardless of Gleason score; D9902B would be initiated, to include subjects with Gleason scores of ≤ 7 . These study populations could not be combined for the efficacy analysis.
30 MAY 2003	Special Protocol Assessment agreement received for Protocol D9902B	Time to objective disease progression and time to disease related pain were co-primary endpoints.
30 JUL 2003	Sipuleucel-T received Fast Track designation for the treatment of asymptomatic patients with metastatic, Gleason Sum ≤ 7 AIPC	Received Fast Track designation based on the potential of sipuleucel-T to prolong TTP and time to disease related pain (TDRP) in men with asymptomatic, metastatic, Gleason Sum ≤ 7 AIPC

BLA 125197, Sipuleucel-T
 CBER Clinical Review

Date	Milestone Description	Outcome
October 2004	D9901 Survival Analysis Performed	Analysis demonstrated a survival increase of sipuleucel-T compared with APC-Placebo in the ITT population
24 NOV 2004	D9902A Final Statistical Analysis Plan submitted to FDA	FDA agreed to the proposed D9902A SAP with primary endpoint of time to disease progression and adding overall survival as secondary endpoint.
28 JUL 2005	Type C Meeting (CMC Licensing Strategy)	FDA agreed that the to-be-licensed manufacturing process is consistent with that used for studies that will serve as the clinical basis for the BLA.
11 OCT 2005	Amendment 7 for Protocol D9902B submitted	Major changes including elevation of survival to the primary endpoint, expansion of the eligibility criteria to include minimally symptomatic patients, and elimination of the Gleason score restriction
25 NOV 2005	SPA agreement for Amendment 7	FDA agreement to above changes
21 Aug 2006	Clinical section of BLA submitted electronically	BLA 125197 filed and BLA review initiated.
29 March 2007	Meeting of CTGT advisory committee to discuss BLA 125197	CTGTAC voted 13-4 that evidence of efficacy had been provided.
8 May 2007	CR letter issued by FDA	Submitted application deemed insufficient to support licensure
9 Jan 2008	SPA amendment submitted	SAP for primary endpoint, revision of interim analysis plan and revised IDMC charter
29 Apr 2008	Type C pre-BLA clinical issues	FDA reached agreement with applicant regarding content of sBLA.
29 Jan 2009	Revised statistical analysis plan submitted to IND 6933 Amd # 279	Revised SAP submitted – FDA accepted changes.
14 April 2009	Revised IDMC charter submitted to IND 6933 Amd # 282	Revised IDMC charter submitted – FDA accepted changes.

Summary of Regulatory History: Originally the co-primary endpoints of study D9902B were TTP (radiological) and time to development of disease related pain; therefore, patients had to be asymptomatic at entry. Enrollment was stratified by bisphosphonate use (bisphosphonate use could have potentially confounded interpretation of the co-primary endpoints) as well as by primary Gleason grade and the number of bone metastases. Following the 2004 analysis of survival results for D9901, protocol amendment 7 (11 Oct 2005) elevated overall survival to primary endpoint in D9902B. FDA agreed to this change in design under a SPA revision on 25 November 2005 which allowed mildly symptomatic patients to be eligible. At the time of Amendment 7 submission in October 2005, only 40% of accrual had occurred. The first interim analysis was performed in May of 2008 after 247 death

events had occurred and accrual had been completed. This analysis showed a HR of 0.8 but did not meet the protocol-defined threshold for stopping.

The initial BLA was submitted 21 August 2006. A review of submitted data, including sensitivity analyses and review of death events supported a finding of an increase in the median survival in the sipuleucel-T arm compared with the APC-Placebo arm in Study D9901. The application was discussed at the Cell Tissue and Gene Therapy Advisory Committee and received a positive recommendation for licensure. However, the lack of a pre-specified primary method for survival analysis rendered it impossible to estimate the Type I error (statistical persuasiveness) for this survival difference. In addition, the six-month difference in median survival times between D9901 and D9902A, despite similar study design, inclusion criteria, and baseline characteristics, suggest that the eligibility criteria did not define a homogeneous population in these small studies. The small population studied and lack of statistical persuasiveness of the submitted information increased the likelihood that the observed survival difference in D9901 might be attributable to chance. FDA decided to defer the licensure decision until mature survival data from the larger ‘pivotal’ study D9902B could be submitted and reviewed. Please see clinical review of original BLA submission, dated 5/8/2007 for additional details.

2.6 Other Relevant Background Information

Since prostate cancer does not occur in the pediatric population, the FDA Pediatric Review Committee (PeRC) recommended that a pediatric waiver be granted for sipuleucel-T.

Reviewer comment: A pediatric waiver is appropriate for this application.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The clinical module and subsequent amendments were submitted electronically. As the BLA review progressed, the applicant submitted amendments, including a required safety update and integrated summaries of effectiveness and safety as well as responses to FDA information requests (IR) as listed in the table below:

Table 5: Summary of BLA amendments

Amendment number	Submission Date	Contents
33	8/10/2009	Clinical module
34	10/30/2009	CMC Module, Integrated summaries of safety and efficacy
35	11/16/2009	Response to FDA statistical request
36	12/23/2009	Safety Data Update
37	2/8/2010	Response to form 483
38	2/12/2010	Response to information request regarding --b(4)----- computer software
39	2/18/2010	Responses to clinical and CMC information requests
40	2/26/2010	Response to pre license Inspection request for information regarding manufacturing deviations

Amendment number	Submission Date	Contents
41	3/2/2010	Response to pre license Inspection request for information regarding manufacturing deviations
42	3/3/2010	Response to clinical request for information

Interim analysis: A planned interim analysis occurred in May of 2008 after 247 death events had occurred. The hazard ratio, 95% confidence intervals were provided to the sponsor by the independent Data Monitoring Committee as per the IDMC charter. Since the primary endpoint was overall survival, accrual was completed and the study remained blinded, FDA does not believe that the study integrity was compromised by this procedure.

Results of BioResearch monitoring:

-----Information withheld per the Privacy Act-----

[Information withheld per the Privacy Act]

3.2 Compliance with Good Clinical Practices

The investigators agreed to conduct the trial in accordance with applicable US regulations and International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP). The clinical review did not identify any substantial deviations from GCP.

3.3 Financial Disclosures

Certification of financial disclosure (Form 3454) was provided by the applicant. Documentation of financial disclosure was provided for all investigators except for three sub-investigators. The applicant made multiple attempts to obtain this information and has stated that no compensation was provided by the applicant to these three sub-investigators. Two other sub-investigators were provided compensation by the applicant for consulting, honoraria, authorship/editing, market research and advisory board participation. FDA does not believe that there is any evidence that financial conflicts may have influenced the results of the study.

Reviewer comment: The data generated by the submitted randomized studies are considered to be acceptable in support of the proposed indication.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Product description:

Sipuleucel-T is manufactured using the patient's own autologous white blood cells, which are collected by leukapheresis and shipped to the manufacturing facility for further processing. At the manufacturing facility, the cells are put through two buoyant density gradient separations intended to -b(4)- red blood cells and granulocytes while retaining leukocytes. PAP-GM-CSF, which consists of the prostatic acid phosphatase (PAP) linked to GM-CSF, is then added to the cells. PAP is a protein present on prostate cells and provides the antigen that is intended to direct the immune system to target prostate cancer. The GM-CSF portion of the protein helps to target the PAP protein to antigen presenting cells and activate those cells. --b(4)-----

----- The cells are cultured in the presence of PAP-GM-CSF for 36-44 hours. After culture, the cells are washed and suspended in Lactated Ringer's solution for infusion back into the patient. Minimal residual levels of the intact PAP-GM-CSF are detectable in the final product.

The course of therapy is 3 doses, given at approximately 2 week intervals. Each leukapheresis produces one dose; therefore, the patient undergoes 3 separate leukapheresis procedures. Each leukapheresis product goes through the identical manufacturing process and to produce a unique lot of sipuleucel-T. If a lot fails to meet requirements for quality, the patient must undergo an additional leukapheresis to make a new lot of product. Each dose is shipped and administered fresh (without cryopreservation) within b(4) hours of manufacture. The lot release testing is performed simultaneous to product shipping. All lot release tests must meet specifications for the product to be infused and that information is sent to the infusion site.

The product has high inherent variability due to the autologous nature of the product, specifically patient-to-patient variability in the cellular composition and total cell number of the leukapheresis. There is also substantial variation with each leukapheresis from the same patient between collections for the 3 different lots. The level of product variability does not extend to all lot release criteria as cell viability is very high and consistent at all stages of manufacturing. The most variable product

attributes are CD54⁺ cell number (-b(4)-), the level of CD54 upregulation (-b(4)---), and in-process -b(4)----- Product lot release specifications were based on a statistical analysis of historical manufacturing data and set around 3 standard deviations from the mean.

Manufacturing controls:

Process and product controls are in place to assure cellular product quality. Quality control testing includes sterility, identity, purity, and potency testing. Lot release is based on a combination of in-process testing results as well as final product testing. PAP-GM-CSF is --b(4)----- The cell lines used were extensively tested and found to be free of viral contamination. In addition, -b(4)---

----- (See separate CMC review for details)

4.2 Preclinical Pharmacology/Toxicology

Due to the autologous nature of sipuleucel-T, limited preclinical studies were conducted in support of this BLA. Pharmacology studies conducted by the sponsor demonstrated that PAP is a potential immune target for prostate cancer active immunotherapy. *In vitro* studies showed that two murine T cell hybridoma cell lines that responded to both murine and human HLA-DR1⁺APCs and recognized two HLA-DR1 restricted PAP-specific epitopes could be established, indicating that human PAP can be taken up, processed and presented in the context of a human MHC class II molecule. *In vitro* analysis of PAP protein or PAP gene expression in human tissues demonstrated high expression of the PAP protein or gene in normal and malignant prostate tissue, with significantly lower expression in a limited set of non-prostate normal tissues. (See separate Pharmacology/Toxicology review for details)

4.3 Statistics

The large randomized, double-blind, well-controlled Phase III study (D9902B) demonstrated that patients with metastatic AIPC who received Sipuleucel-T had improvement in overall survival, compared with those who received placebo. The finding was also supported by the other two small randomized trials (D9901, D9902A). The efficacy results from the three randomized trials support the claim of using Sipuleucel-T for the treatment of men with asymptomatic or minimally symptomatic metastatic AIPC. See separate Statistics review.

4.4 Epidemiology

A possible safety signal of increased risk of cerebrovascular events (CVE's) was identified. The applicant will therefore be required to conduct a postmarketing study based on a registry design to assess the risk of cerebrovascular events in at least 1,500 patients with prostate cancer who receive sipuleucel-T. See separate Office of Biometrics and Epidemiology (OBE), Division of Epidemiology (DE) review memo regarding pharmacovigilance planning.

5. Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 6: Summary of Clinical Studies

Study #	Study Type	Primary Study Endpoints	Study Design	Population	Product, Dosage, Route of Administration, and Schedule	# of Subjects	Status
D9902B	P3	OS	Placebo-controlled, double-blind, multi-center, randomized (2:1)	Asymptomatic or minimally symptomatic metastatic CRPC	Sipuleucel-T or placebo, with a minimum of 20×10^6 CD54+ cells/dose, i.v. at Weeks 0, 2, & 4	512 (341 Sipuleucel-T: 171 Placebo)	Closed
D9901	P3	TTP OS was not a pre-specified endpoint	Placebo-controlled, double-blind, multi-center, randomized (2:1)	Asymptomatic metastatic CRPC	Sipuleucel-T or placebo, with a minimum of 3×10^6 CD54+ cells/dose, i.v. at Weeks 0, 2, & 4	127 (82 Sipuleucel-T: 45 Placebo)	Complete
D9902A	P3	TTP (OS revised secondary endpoint following analysis of D9901)	Placebo-controlled, double-blind, multi-center, randomized (2:1)	Asymptomatic metastatic CRPC	Sipuleucel-T or placebo, with a minimum of 3×10^6 CD54+ cells/dose, i.v. at Weeks 0, 2, & 4	98 (65 Sipuleucel-T: 33 Placebo)	Complete
P-11	P3	Time to Biochemical failure (PSA ≥ 3 ng/mL)	Placebo-controlled, double-blind, multi-center, randomized (2:1)	Non-metastatic prostate cancer with PSA progression following radical prostatectomy	Sipuleucel-T or placebo, with a minimum of 3×10^6 CD54+ cells/dose, i.v. at Weeks 0, 2, & 4, revised dose to 20×10^6 CD54+ cells/dose in Dec 2003. Optional single booster dose at time of PSA progression	176	Closed to accrual, with ongoing follow-up for secondary endpoints
PB01	P2	Safety	Open-label, multi-center, salvage	Metastatic CRPC subjects of placebo arm of D9902B with objective disease progression	APC8015F (prepared from cryopreserved PBMC's), minimum of 3×10^6 CD54+ cells/dose, i.v. at Weeks 0, 2 & 4	113	Closed

5.2 Review Strategy

This BLA efficacy review is based primarily on data from Study D9902B with supporting information from Studies D9901 and D9902A. For Study D9902B, survival information was confirmed using CRFs, data set for primary efficacy analyses (KEYVAR2B), death certificates, and SSDI. Subject eligibility was confirmed using CRF, laboratory data, data sets for primary efficacy analysis (KEYVAR2B), and Listings 16.2.8 and 16.2.2 in the BLA submission. The current reviewers also considered the results of the 2007 review by Ke Liu, M.D., Ph.D., of the original BLA submission.

The safety review of this BLA was primarily based on the safety data from four randomized, placebo-controlled studies (D9901, D9902A, D9902B, and P-11). The review material includes the safety data sets and additional amendments submitted to the BLA. See Section 7.1 for details regarding the safety review materials and methods.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study D9902B

The final study protocol is summarized below:

Study Title: A Randomized and Double Blind, Placebo-Controlled Phase 3 Trial of Immunotherapy with Autologous Antigen Presenting Cells Loaded with PA2024 (Provenge®, Sipuleucel-T, APC8015) in Men with Metastatic Androgen Independent Prostatic Adenocarcinoma.

Study Objectives

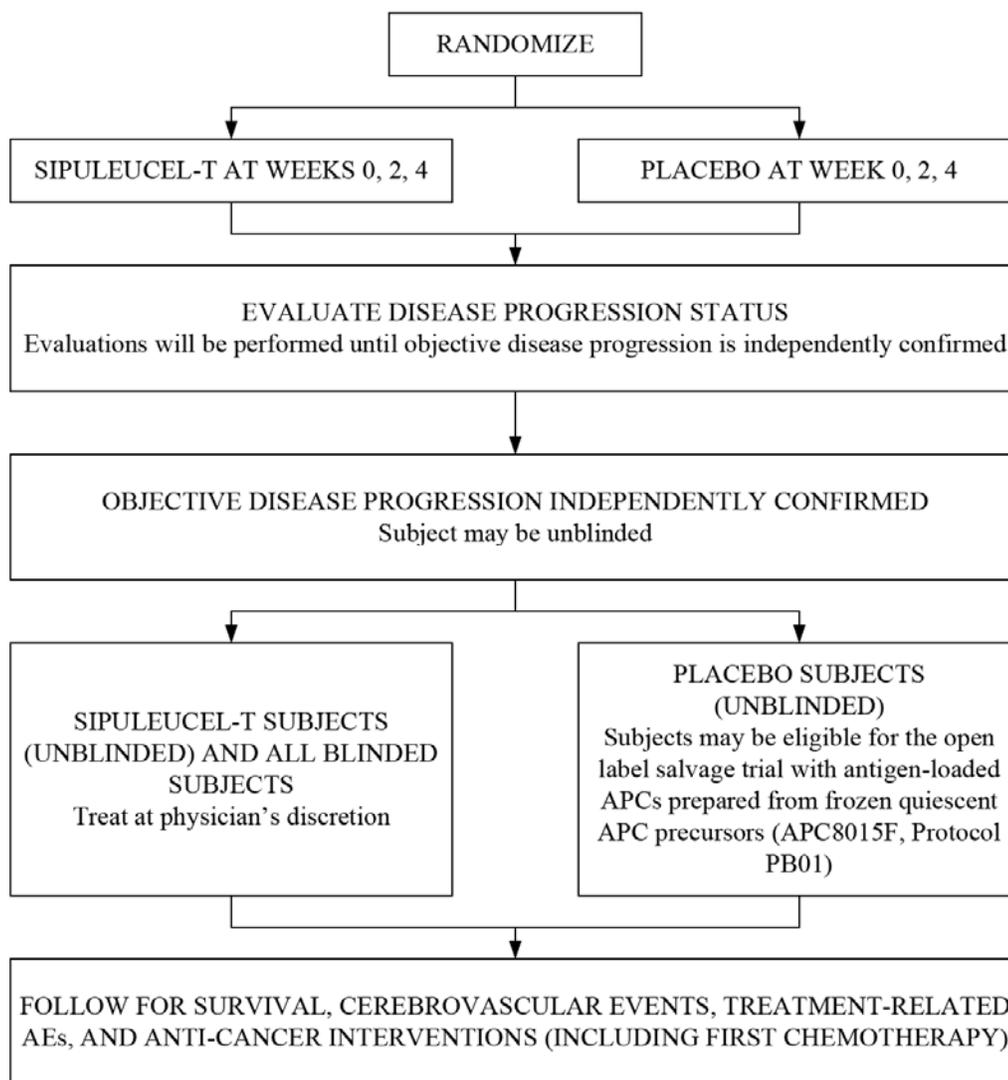
Primary Objective: To assess the safety and efficacy of sipuleucel-T in prolonging survival of men with metastatic androgen independent prostate cancer.

Secondary Objective: To assess the safety and efficacy of sipuleucel-T in delaying time to objective disease progression.

Tertiary Objective: To assess the effect of sipuleucel-T in delaying time to clinical progression, increasing PSADT and generating an immune response.

Study Design: Study D9902B is a randomized, double-blind, placebo-controlled, multi-center study in men with minimally symptomatic or asymptomatic metastatic hormone-refractory prostate cancer. Subjects were randomized (2:1) to receive three doses of either sipuleucel-T or APC-placebo intravenously at Weeks 0, 2, and 4. Subjects who experienced objective disease progression as determined by independent radiology review were unblinded to allow eligible subjects on the placebo arm to cross over to receive APC8015F under a salvage protocol (PB01). After independently confirmed objective disease progression, subjects were allowed to receive additional anti-cancer interventions, at the physician's discretion. Long term follow-up for each subject was until death.

Figure 1: Study D9902B Overall Schema



Eligibility Criteria

Key Inclusion Criteria

- Histologically documented adenocarcinoma of the prostate.
- Evidence of metastatic disease in the soft tissue and/or bone as established by CT scan of the abdomen and pelvis and/or bone scan.
- Evidence of disease progression of androgen independent prostate cancer concomitant with surgical or medical castration. Disease progression was evaluated based on any or all of the following parameters:
 - PSA progression
 - Progression in measurable disease
 - Progression in non-measurable disease
- Serum PSA of ≥ 5.0 ng/mL

- Castration levels of testosterone of <50ng/mL

Key Exclusion Criteria

- Liver, lung, or brain metastases, malignant pleural effusions, or malignant ascites.
- Moderately or severely symptomatic metastatic disease as defined by either criterion:
 - Requirement for opioid analgesic within 21 days prior to registration
 - Average weekly pain score ≥ 4 on a 10-point Visual Analog Scale (VAS) on the Registration Pain Log.
- Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2
- Use of non-steroidal anti-androgens.
- Chemotherapy treatment within 6 months of registration, with the following exception:
- Chemotherapy treatment ≥ 3 months prior to registration is allowed if all of the following criteria are met:
 - Post-chemotherapy PSA was greater than the pre-chemotherapy PSA or the nadir PSA achieved during chemotherapy.
 - Post-chemotherapy bone scan is not improved in comparison to the pre-chemotherapy bone scan.
 - Post-chemotherapy imaging (CT or other modalities) for subjects with nodal disease must not show a decrease in size or number of pathologically enlarged lymph nodes in comparison to the pre-chemotherapy imaging studies.
 - ≥ 2 chemotherapy regimens received prior to registration.
- Initiation or discontinuation of bisphosphonate therapy within 28 days of registration.
- Treatment with any of the following medications or interventions within 28 days of registration:
 - Systemic steroids
 - External beam radiation therapy or surgery
 - Any other systemic therapy or any other investigational product for prostate cancer.
 - Pathologic long-bone fractures, imminent pathologic long-bone fracture (cortical erosion on radiography > 50%), or spinal cord compression.

Treatment Plan

Leukapheresis

Leukapheresis will be done on Weeks 0, 2, and 4 and cells transported to the manufacturing facility for manufacturing of either sipuleucel-T or APC Placebo. The cell product is released 2-3 days after leukapheresis for infusion of sipuleucel-T or APC Placebo to the subjects.

Infusion procedure:

30 minutes prior to infusion, subjects must be pre-medicated with acetaminophen and diphenhydramine. Infusion of the cell product must begin prior to the labeled expiration time. Infusion is done over 60 minutes. Infusion rates may be modified for subsequent infusions if the subject experiences pyrexia and/or rigors. Post-infusion follow-up is 30 minutes.

Ancillary Therapy:

When appropriate, subjects must receive full supportive care, including transfusions of blood and blood products, antiemetics, and antibiotics. Subjects who require systemic therapy for prostate cancer prior to objective disease progression (but based on clinically significant disease specific events or rapidly rising PSA) should remain on study and continue their evaluations for objective disease progression.

Treatment and Unblinding

Following independent confirmation of objective disease progression, subjects may be unblinded to determine treatment assignment. Subjects who received placebo have the option of receiving APC8015F under salvage protocol PB01.

Efficacy Assessments

Active assessments:

Restaging Bone Scans will be performed 6 weeks after the first infusion and at Weeks 10, 14, 18, 22, 26, and 34.

Restaging CT scans will be performed at Weeks 6, 14, 26, and 34.

Evaluation for clinical progression at the time of scheduled study clinic visits at Weeks 2, 4, 6, 14, 26, and 34, or as clinically indicated.

Evaluations for clinical progression (or as clinically indicated), bone scans, and CT scans will be obtained every 12 weeks after Week 34.

Evaluations for clinical progression and imaging studies are no longer required when objective disease progression is independently confirmed.

Confirmation of Complete Response (CR) or Partial Response (PR) by imaging studies will be repeated ≥ 4 weeks later to confirm the response.

For additional details please refer to Table 10.

Efficacy definitions

Overall Survival: Time from randomization until death due to any cause.

Response criteria:

Determined by evaluation of measurable disease, non-measurable disease, and by clinical assessment. Responses are categorized as Complete responses (CR), Partial responses (PR), or Stable disease (SD).

Objective Disease Progression:

Must be confirmed by central imaging review facility.

Definition of objective disease progression will be based on measurement of the index lesion, non-index lesion, bone disease, and appearance of new pathological fracture.

PSA will not be used to assess objective disease progression.

Determination of objective disease progression is to be made by the WHO criteria. ⁹

Humoral Response: Serum antibody titers will be determined using enzyme-linked immunoabsorbent assay (ELISA).

Cellular Response: Proliferation Assays and Enzyme linked immunospot (ELISPOT) assay.

Safety Assessments

Safety Monitoring

Beginning at Week 6, subjects will be monitored every four weeks (clinic visit or telephone calls) for the occurrence and severity of adverse events (AE's) until the objective disease progression endpoint is independently confirmed.

At 2 and 6 months after objective disease progression is confirmed and every 3 months thereafter, subjects will be monitored for survival and evaluated for AEs that are related to the investigational product.

Long term follow-up:

Long term follow-up includes monitoring of CBC's, all cerebrovascular events, treatment-related AE's, and survival. Long term follow-up begins for all subjects, irrespective of the treatment arm, after the subject meets objective disease progression endpoint and exits from the active assessment portion of the trial, and will continue until death.

Upon entering long term follow-up, visits will occur at months 2 and 6 after meeting objective disease progression and every three months thereafter.

Analytical Plan

Study D9902B is designed to be a stand-alone study and will be analyzed separately from Study D9902A.

Randomization Scheme: Assignment to the treatment arms will use the Pocock minimization method¹⁰ to balance the two treatment groups with regard to stratification factors of:

- Primary Gleason Grade (≤ 3 , >4)
- The number of bone metastases (0-5, 6-10, >10)
- Bisphosphonate use (yes, no)

Efficacy Analysis:

Primary Efficacy Variable: Overall Survival (OS) in the Intent-to-Treat population

Primary Efficacy Analysis:

Significance level for final analysis using a 2-sided p-value is allocated to the final analysis based on the O'Brien-Fleming alpha spending function.¹¹ Statistical significance is achieved if the difference in OS between the two treatment groups is less than the pre-specified significance level. Primary test for OS data will use the Wald's test based on the stratified Cox regression model adjusted for two covariates, PSA and LDH. Stratification variables (above) will be included in the analysis.

Censoring for OS analysis (see Appendix C)

Supportive analysis:

Will be conducted based on only those subjects without any missing baseline covariates.

p-value associated with the log-rank, stratified by the above-mentioned stratification variables will be determined. Hazard ratio, with its 95% CI derived from stratified unadjusted Cox regression model, will be provided.

Additional Analyses: will be conducted if there are more than 304 death events in the final database.

Interim Analysis (IA):

One IA is planned when approximately 228 death events (75% of the total number of expected death events) have been observed.

Significance level, using a 2-sided p-value, is allocated to the interim analysis based on the O'Brien-Fleming alpha spending function.

Statistical significance is achieved if the difference in OS between the two treatment groups is less than the pre-specified significance level.

Secondary Efficacy Variable: Time to Objective Disease Progression - defined as time from randomization to achieving objective disease progression, as determined by the IRRC. Death events will be considered a competing event.

Tertiary Efficacy Variables: Time to clinical progression, PSA doubling time, and immune response.

5.3.2 Supportive Studies

D9901: Study D9901 screened 186 patients to enroll 127 subjects. Eighty-two were randomized to the sipuleucel-T arm and 45 to the APC-Placebo arm. Some imbalances were noted in the baseline demographic and prognostic characteristics, including Gleason grading and disease location (bone, soft tissue, or both), between the two arms. Sensitivity analyses did not suggest that these imbalances confounded the survival results. The results of the primary efficacy analysis of D9901 showed that the study did not achieve its primary objective of prolonging time to objective disease progression or any other pre-specified efficacy endpoint. The estimated median time to disease progression was 11.0 weeks in the sipuleucel-T arm compared to 9.1 weeks in the APC-Placebo arm. This 1.9-week delay in the time to objective disease progression did not reach statistical significance ($p = 0.085$). Although the protocol did not pre-specify a primary method for survival analysis, a 3-year survival analysis of D9901 was performed as part of the follow-up. The analysis showed that the median survival times in the subjects treated with sipuleucel-T and APC-Placebo were 25.9 and 21.4 months, respectively, a difference of 4.5 months. Overall survival difference reached statistical significance ($p = 0.010$) by a log rank test. The unadjusted HR was 1.71 [95% confidence interval (CI): 1.13, 2.58]. Study D9901 did not reach statistical significance with regard to the primary efficacy objective, but a post hoc analysis demonstrated prolonged survival in the sipuleucel-T-treated subjects, which was the basis for the initial BLA efficacy claim.

D9902A: The D9902A trial was originally designed to be a companion trial to D9901: eligibility, endpoints, treatment plan, monitoring, accrual goals, and statistical analysis plans were initially the same in both studies. Study D9902A was terminated early because of the overall negative findings from D9901. Ninety-eight patients were enrolled out of a planned 120 patients: 65 were randomized to receive sipuleucel-T and 33 to APC-Placebo. As a result of this early termination, D9902A was

underpowered to assess its primary endpoint of improved time to progression. The estimated median time to disease progression in D9902A was 10.9 weeks in the sipuleucel-T arm compared with 9.9 weeks in the APC- Placebo arm ($p=0.72$); median survival times were 19.0 months and 15.7 months, respectively ($p = 0.331$, log rank test).

Study P-11: This was a randomized, double-blind, placebo-controlled trial investigating the safety and efficacy of sipuleucel-T in earlier stage prostate cancer, enrolling subjects who experience PSA elevation following radical prostatectomy. Subjects were eligible after a 13-week open-label treatment with a luteinizing hormone-releasing hormone-analogue (LHRH-a) in order to normalize the prospective subject population to a common baseline PSA level of < 1 ng/mL. Following the run-in period, eligible subjects were randomized to blinded treatment assignments of either sipuleucel-T or placebo in a 2:1 ratio. Stratification was based on receipt of adjuvant or salvage radiation therapy after prostatectomy (Yes or No) and Gleason score (≤ 6 or ≥ 7). Subjects underwent three leukapheresis procedures on alternate weeks (Weeks 0, 2, and 4); approximately two days following each leukapheresis procedure, subjects received an infusion of either sipuleucel-T or placebo.

The endpoint for the treatment and observation period was biochemical failure, which was the time when the subject's PSA had risen to ≥ 3 ng/mL. During this period, safety was evaluated by collecting AEs and by performing physical examinations and laboratory evaluations; subjects were monitored for safety from the time of randomization, at Weeks 0, 2, 4, 8, 13, and 26, and every three months thereafter until biochemical failure. At the time biochemical failure was confirmed, subjects were eligible for a booster infusion. The booster process consisted of one leukapheresis procedure followed approximately two days later by one infusion of the same treatment, sipuleucel-T or placebo, as assigned at randomization. Subjects were not unblinded.

The endpoint for the surveillance period was documentation by bone or computed tomography (CT) scan of metastatic disease (distant failure). During the surveillance period, subjects continued to be evaluated periodically for safety and efficacy endpoints; subjects were monitored for safety at 3, 6, and 12 months following biochemical failure, and every year thereafter until distant failure. Following confirmed distant failure, subjects entered the survival period and were evaluated periodically for safety and survival.

6 Review of Efficacy

6.1 Efficacy Summary

Study D9902B was a randomized, double-blind, adequate and well-controlled Phase 3 study (D9902B) which randomized 512 that patients with hormone refractory prostate cancer in a 2:1 ratio to receive sipuleucel-T (n=341) or placebo control (n=171). The primary analysis showed that treatment with sipuleucel-T was associated with a statistically significant improvement in overall survival compared with the group of patients given placebo control. Median survivals were 25.8 months on the sipuleucel-T arm vs. 21.7 months in the control arm, an average of 4.1 months longer survival in the group of subjects who received sipuleucel-T. The finding was supported by a variety of sensitivity and subgroup analyses and by analysis of two smaller randomized trials (D9901 and D9902A).

6.2 Indication studied

The initial proposed indication was the treatment of men with metastatic castrate resistant (hormone refractory) prostate cancer. The population studied had metastatic, androgen independent prostatic adenocarcinoma which was asymptomatic or minimally symptomatic.

Reviewer's comment: The population identified for this indication is appropriate. Study D9902B was conducted in the asymptomatic and minimally symptomatic group of subjects. No data exists for its use in moderately or severely symptomatic subjects. Therefore generalization of the labeled indication to metastatic androgen independent prostatic adenocarcinoma, would be based on extrapolation of data from the asymptomatic or minimally symptomatic group. Moreover pain related to prostate cancer is considered a prognostic factor in metastatic prostate cancer. Subjects with pain tend to have higher tumor burden. Generalization of the labeled indication to metastatic androgen independent prostatic adenocarcinoma would expose a population of subjects with higher disease burden with adverse prognostic factors (moderately and severely symptomatic subjects) to a therapy with no known benefit in this subgroup of subjects and with the associated risks of delay in time to subsequent docetaxel therapy (effective therapy for symptomatic metastatic) and inherent risks of leukapheresis.

6.3 Methods

The data from the single pivotal randomized phase 3 trial D9902B was used for the evaluation of efficacy. Analyses of Studies D9901 and D9902A supported this assessment.

6.4 Demographics

Table 8 summarizes the demographics and baseline characteristics of the subjects included in the primary efficacy analysis population.

Table 7: Summary of Demographics and Baseline Characteristics

Baseline Characteristics	Sipuleucel-T (n=341) (Range) [%]	Placebo (n=171) (Range) [%]
Median Age (in yrs)	72 (40-89)	70 (40-89)
Weight (in lbs)	194 (115-384)	190 (132-300)
Race		
Caucasian	305 [89]	156 [91]
Black or African-American	23 [6.7]	7 [4]
Asian	2 [0.5]	2 [1.2]
Hispanic	10 [2.9]	6 [3.5]
Other	1 [0.3]	0
Time from diagnosis to randomization (in yrs)	7.11 (0.84-24.5)	7.11 (0.92-21.5)
Gleason sum score \leq 7	257 ¹ [75.4]	129 ² [75.8]
ECOG status 0	279 [81.8]	139 [81.3]
No pain at baseline	175 ³ [51.3]	90 [52.6]
Site of disease localization ⁴		
Bone lesions only	173 [50.7]	74 [43.3]
Soft tissue lesions only	24 [7.04]	14 [8.19]
Soft tissue & Bone lesions	143 [41.9]	83 [48.5]
Castration only	62 [18.2]	30 [17.6]
Complete Androgen Blockade	279 [81.8]	141 [82.5]
Prior Chemotherapy	67 [19.7]	26 [15.2]
Prior Docetaxel therapy	53 [15.5]	21 [12.3]
Prior Orchiectomy	32 [9.4]	13 [7.6]
Prior Radiotherapy	185 [54.3]	91 [53.2]
Radical Prostatectomy	121 [35.5]	59 [34.5]

* All data have been derived from the efficacy analyses data set "KEYVAR2B" submitted by the applicant.

1= One subject had Total Gleason (GS) score of 4.

2= Subject ID# 92048-0910: Total GS Score was not available on CRF review; the Primary Gleason Score was 3.

3= Three subjects had missing information in the data sets (KEYVAR2B) for pain. On CRF review, one subject (Subject ID# 92012-0685) had no pain; one subject (Subject ID 92012-0846) had minimal pain; and one subject (Subject ID# 92024-1019) was imputed to have minimal pain since the CRF review of this subject confirmed that the subject did not have moderate or severe pain at baseline.

4= One subject in the sipuleucel-T arm (Subject ID# 92038-0525) did not have localization of disease listed in the data set. CRF review showed that imaging studies were done, alkaline phosphatase was elevated to 2031U/L, and inclusion criteria checklist indicates that the subject had bone and/or soft tissue disease and PSA progression. The subject has been excluded from this table for site of localization.

Reviewer comments: The subjects in both arms were fairly well balanced for age, race, duration of disease, Gleason sum score, ECOG status, castration, and complete androgen blockade. Imbalances between the two arms were noted for bone only disease, bone and soft tissue disease, and prior chemotherapy (including docetaxel therapy). Many patients in Study D9902B with soft tissue disease had primarily lymph node involvement. More subjects in the sipuleucel-T arm received prior chemotherapy, including docetaxel therapy. An analysis to assess the effect of this imbalance on the study outcome was not performed. However, the number of subjects who received prior chemotherapy was too small to permit a meaningful analysis of the effect of the imbalance on the study outcome.

Table 9 summarizes those laboratory values evaluated at the time of enrollment that were important, either from a prognostic standpoint, or based on the product’s mechanism of action. Alkaline phosphatase, hemoglobin, LDH, and PSA are prognostic factors in patients with hormone refractory prostate cancer. WBC and serum PAP are specific laboratory values that are related to the proposed mechanism of action of sipuleucel-T.

Table 8: Summary of Baseline Laboratory Values, Intent-to-Treat Population.

Laboratory Evaluation	Sipuleucel-T (n=341) Median	Placebo (n=171) Median	Normal Range
Alkaline Phosphatase (U/L)	99	109	31-131
Hemoglobin (g/dL)	12.9	12.7	12.5-18.1
Serum LDH (U/L)	194	193	53-234
Serum PSA (ng/mL)	51.71	47.19	≤ 2.7 - ≤ 7.2 (Age-dependent cut-off values)
Serum PAP (U/L)	2.7	3.2	0.1-1.2
White Blood Cell count (10 ³ /μL)	6.15	5.98	3.8-10.7
Lymphocyte count (10 ³ /μL)	1.44	1.41	0.8-3.0

Reviewer’s comment: As shown in Table 9, there appears to be a slight imbalance in the baseline median PSA; however, the difference between the two arms was marginal (4.5 ng/dL), and unlikely to have a substantial effect on the study results.

Halabi scores are used in patients with metastatic hormone resistant prostate cancer to predict the overall survival probability, and are based on a multivariate model of pre-treatment factors, including serum LDH, PSA, alkaline phosphatase, hemoglobin, Gleason sum score, ECOG performance status, and visceral disease.

Table 9: Predicted Survival by Treatment based on Halabi Scores

	Sipuleucel-T (N = 341)	Placebo (N = 171)
Median(HALABI)	20.3	21.2

Reviewer’s comment: The two study arms are well-balanced for predicted mortality based on the Halabi scores. The balance in Halabi scores in the two arms indicates that the randomization was successful in providing two groups with similar predicted overall survival.

Table 10: Summary of Baseline Stratification Factors, ITT Population*

Stratification Factor	Sipuleucel-T (n=341) (%)	Placebo (n=171) (%)
Primary Gleason Grade		
≤ 3	144 (42.2)	71 [41.5]
≥ 4	197 (57.8)	100 [58.5]
Bone Metastases		
0-5	146 (42.8)	73 [42.7]
6-10	49 (14.4)	25 [14.6]
>10	146 (42.8)	73 [42.7]
No	177 (51.9)	89 [48.5]
Yes	164 (48.1)	82 [47.9]

Applicant's data set used to generate data set analyzed by reviewer: KEYVAR2B

Clinical reviewer's data set generated for review of Placebo group: BaselineStratFactors.Placebo.KEYVAR2B

Clinical reviewer's data set generated for review of Sipuleucel-T group: BaselineStratFactors.Sip-T.KEYVAR2B

Reviewer's comments: Of the three baseline stratification factors, two are known to be of prognostic value for survival of patients with metastatic prostate cancer. Higher primary Gleason Grade is a known negative prognostic factor with regard to development of bony metastases or death from prostate cancer.¹² The stratification of subjects prior to study entry, based on the extent of disease (EOD) on initial bone scan, is also supported by referenced literature. However, the applicant's stratification for bone metastases using groups based on 6-10 lesions differs from the Soloway system, which uses groups based on 6-20 lesions and >20 lesions.¹³ Nevertheless, the stratification factor is valid in the context of this minimally symptomatic and asymptomatic population. The independent prognostic effect of bisphosphonate use in prostate cancer on overall survival is not clear; therefore, the importance of bisphosphonate use as a stratification factor is unclear. The randomization process was successful in producing balance in the stratification factors between the both arms.

Reviewer's comment regarding limitations of the prognostic data: In general, the number of positive nodes is a prognostic factor for time to symptomatic progression and tumor-related deaths.¹⁴ Assessment of the number of involved lymph nodes at baseline was not included in the protocol. Therefore, analysis of the data for any imbalance in the number of lymph nodes involved, in subjects with only soft tissue disease, or in subjects with both soft tissue and bone disease, could not be performed.

6.5 Subject Disposition

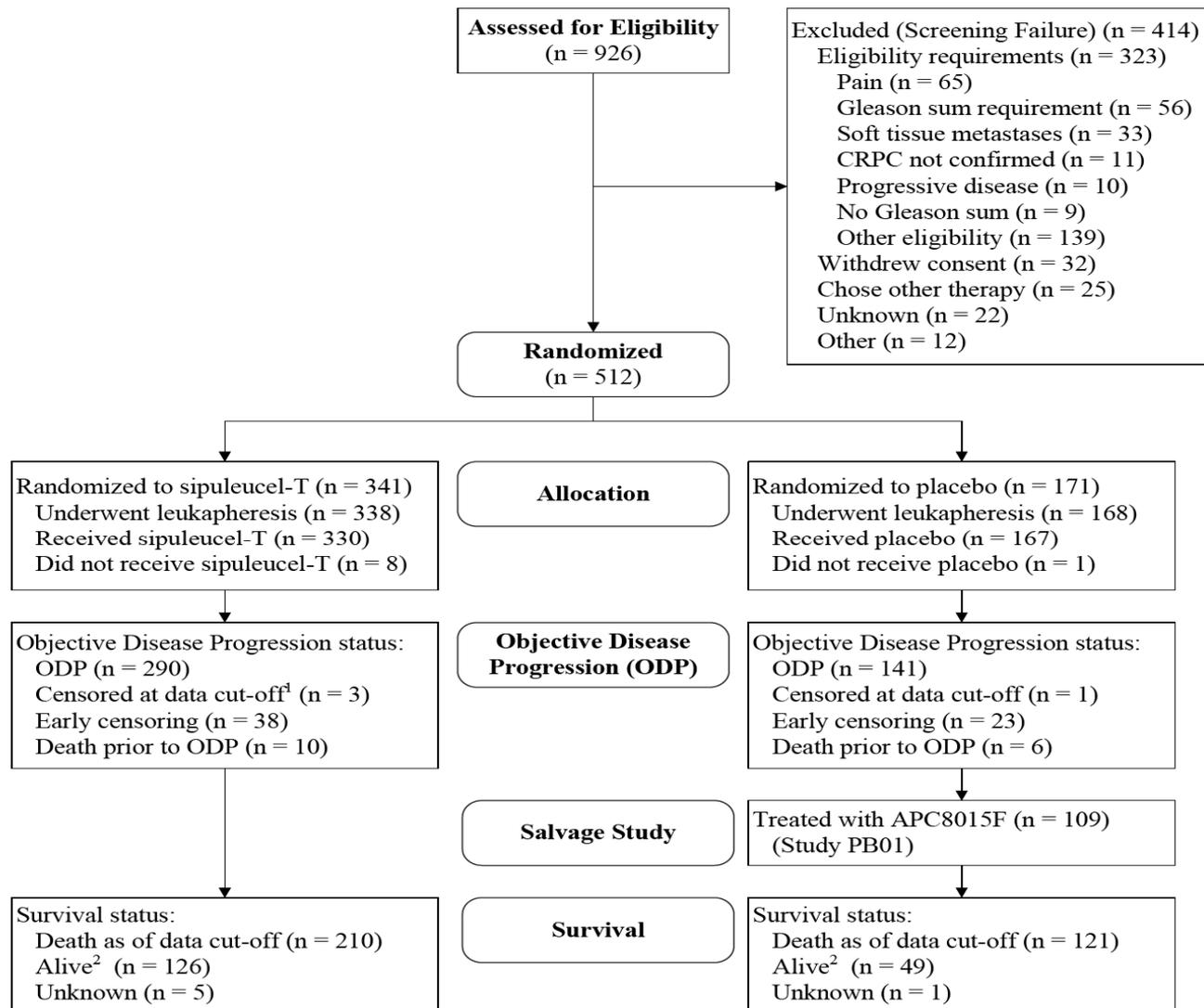
- 926 subjects were screened for eligibility; 414 were screening failures.
- 512 subjects were randomized between August 29, 2003 and November 9, 2007, across 75 clinical trial sites.
- 314 subjects were randomized to sipuleucel-T and 171 to the placebo arm.
- 506 subjects underwent at least one leukapheresis, and 497 subjects underwent at least one infusion.

BLA 125197, Sipuleucel-T
CBER Clinical Review

- 3 subjects in each arm did not undergo leukapheresis; of these, four had venous access problems; one subject withdrew consent; and one subject developed brain metastases prior to leukapheresis.
- 9 subjects who underwent leukapheresis did not receive infusions:
 - 6 subjects randomized to sipuleucel-T had product that failed product quality control.
 - 1 subject randomized to sipuleucel-T was unable to complete leukapheresis related to poor venous access.
 - 1 subject randomized to sipuleucel-T experienced a leukapheresis-related adverse event.
 - 1 subject randomized to placebo had visible white fibers, that would not dissipate, in the product.
- Of the 512 subjects randomized, 331 (64.6%) of subjects died as of the data cut-off date (18 January 2009). Death occurred in 210 (61.6%) subjects in the sipuleucel-T arm, and 121 (70.8%) subjects in the placebo arm. Of the 181 subjects alive at final analysis, five subjects (two randomized to sipuleucel-T and three randomized to placebo) died after the cut-off date. Six subjects considered to be alive for the final analysis had an unknown survival status as of the survival sweep cut-off date (12 January 2009), with four of these subjects (three randomized to the sipuleucel-T arm and one to the placebo arm) having a survival follow-up of < 6 months, and two of these subjects having a substantial follow-up of 20.6 months and 37.8 months.

Figure 7 provides further details of subject disposition:

Figure 7: Subject Disposition



¹ The data cut-off date was 18 JAN 2009.

² Last contact occurred after beginning of survival sweep (12 JAN 2009).

Protocol Deviations:

- Major Protocol Deviations identified included those deviations related to key eligibility criteria (including pain at entry, adequacy of castration, location of metastatic sites) and deviations related to documentation of the date of death.
- Minor Protocol Deviations were any deviations from the protocol that were not major protocol deviations.

Method of identifying major protocol deviations:

Major eligibility deviations were identified and reviewed by the clinical reviewer using the CRFs and the listing of protocol deviations provided in the CSR. These

were compared with the listing of major protocol deviations provided in the data sets used in the primary efficacy analysis.

To ensure that eligibility criteria were met, serum testosterone levels were verified using the laboratory values provided in the CRFs and comparing these values to the CSR listing.

For additional details of the major protocol deviations based on subject ID, please see Appendix D.

Major protocol deviations occurred in 2.7% (14 of 512) of subjects in the study.

Table 11: Major Protocol Deviations

Description of Deviation	Deviation type	Sipuleucel-T	Placebo
Lung metastases	Exclusion criterion	1	0
Adequate liver function	Inclusion criterion	1	0
Basal cell carcinoma, disease free for ≥ 3 years	Exclusion criterion	1	0
Symptomatic metastatic disease	Exclusion criterion	2	3
Androgen independence not verified	Inclusion criterion	1	
Not on medical castration therapy at the time of study entry	Inclusion criterion	0	1
Adequate evidence of castration	Inclusion criterion	1	0
Serum testosterone levels < 50 ng/dL	Inclusion criterion	2	1

Randomization and Death Data:

Review of the death data identified a few discrepancies between the applicant’s data sets and the source documents that were used to confirm the date of death. Forty-nine subjects had discrepancies (see Appendix D) that were related to either randomization dates or dates of deaths. These discrepancies were discussed with the applicant. The responses and the supporting documentation submitted under Amendment 036 (12/22/09) were considered adequate to allow inclusion of 47 of these subjects in the primary efficacy analysis. Two subjects had dates of deaths that were different from that reported in the primary efficacy data sets.

Reviewer’s comments: The applicant’s response provides sufficient information to complete the review of data. The verification provided is adequate. Date of deaths provided in this response was compared with those in the primary efficacy data set provided by the applicant, and two discrepancies were noted.

6.6 Analysis of Primary Endpoint(s)

6.6.1 Interim analysis

Interim Analysis of the Primary Efficacy Endpoint in the Intent-to-Treat Population:

An interim analysis was done using the visit cut-off date of May 28, 2008, with 247 death events occurring prior to this date. Details of the interim analysis that were available to the sponsor included the Hazard Ratio: 0.08 with the 95% CI: 0.610-1.051.

Reviewer's comments: The IDMC charter version 4, submitted to the FDA, specifies that the IDMC will provide overall survival results (hazard ratio, 95% confidence interval) to the applicant. The study was closed to accrual before the date of the interim analysis. The annual report submitted in March 2008, confirms that the study was closed to accrual, and 466 subjects had received at least one infusion of sipuleucel-T or placebo. No protocol modifications were made subsequent to the submission of the interim analysis data; therefore, the integrity of the conduct of the study was maintained. In addition, the interim analysis did not result in unblinding of any of the study participants to treatment allocation for individual subjects; maintenance of the blind decreases the risk that management of the subject would be biased by the results of the interim analysis. Also, survival, the primary efficacy outcome measure, is relatively resistant to biased assessment. Furthermore, this review included confirmation of subject deaths by examination of death certificates and Social Security death indices. In summary, the applicant's access to the results of the interim analysis is unlikely to have compromised the study integrity or the results of the primary efficacy analysis.

6.6.2 Primary analysis

Primary Analysis of Overall Survival:

The primary analysis of OS used a 2-sided Wald's test to detect a treatment effect based on a stratified Cox regression model adjusted for the two baseline covariates of PSA and LDH and stratified by the three randomization factors of primary Gleason grade, number of bone metastases, and bisphosphonate use, conducted in the intent-to-treat (ITT) population, when 210 of 341 (61.6%) subjects in the sipuleucel-T arm and 121 of 171 (70.8%) subjects in the placebo arm died. As specified in the protocol, the timing of the primary analysis was determined by the total number of events. The estimated median follow-up times were 33.7 and 35.9 months in the sipuleucel-T and placebo arms respectively. An interim analysis had been conducted; therefore, the significance level for the final analysis was adjusted from a p-value of 0.05 to 0.043. The results of the sponsor's primary analysis were confirmed by the FDA statistical reviewer and are presented in Table 13 below:

Table 12: Primary Analysis of Overall Survival.

	Sipuleucel-T (n=341)	Placebo (n=171)
Censored n (%)	131 (38.4)	50 (29.2)
Censored prior to survival sweep ^a	5 (1.5)	1 (0.6)
Events n (%)	210 (61.6%)	121 (70.8)
Median Survival Time (months) (95% CI)	25.8 (22.8, 27.7)	21.7 (17.7, 23.8)
Median Follow-up Time		
Observed	20.6	19.3
Estimated ^b	33.7	35.9
Primary Model ^c		
p-value	0.032	
HR (95% CI)	0.775 (0.614, 0.979)	
Unadjusted Analysis ^d		
p-value	0.023	
HR (95% CI)	0.766 (0.608, 0.965)	

a: 4 of these subjects had less than 6 months follow up (3 randomized to the sipuleucel-T arm and 1 to the control arm)

b: From reverse Kaplan-Meier method treating death event as censored

c: From a Cox regression model with treatment, PSA and LDH as the independent variables, stratified by randomization strata

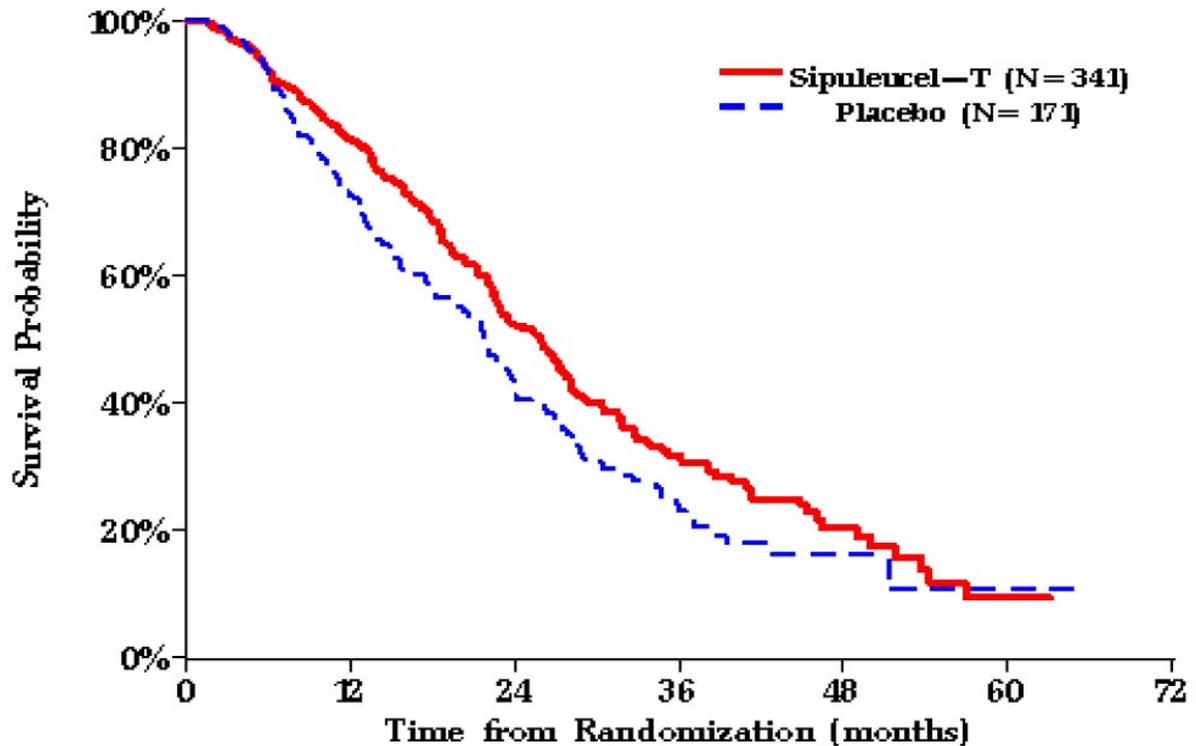
d: p value obtained from log rank test, and HR obtained from a Cox regression model with treatment as the independent variable, both stratified by randomization status

The results of the primary analysis of OS, with a p-value=0.032, with an HR of 0.775, met the pre-specified statistical criterion (p=0.043) for statistical significance for the final analysis. Median survival time was 4.1 months longer in the sipuleucel-T arm compared to the control arm (25.8 versus 21.7 months).

Reviewer's comments: The primary efficacy analysis demonstrates a statistically significant difference in favor of sipuleucel-T. The hazard ratio of 0.775 and the 95% confidence interval (0.614, 0.979) based on the primary analysis model suggest a decreased risk of death in favor of sipuleucel-T. The improvement in median overall survival time was 4.1 months which is a clinically meaningful improvement.

The FDA statistical reviewer's Kaplan Meier Plot generated from the overall survival data in the intent to treat population is presented in Figure 2 below:

Figure 2: Kaplan-Meier Analysis of Overall Survival (ITT Population)



Reviewer's comments: The curves seem to separate at around 7-9 months suggestive of a delayed effect of sipuleucel-T on survival, however median time to docetaxel therapy in the sipuleucel-T group was 7.2 months and those in the placebo arm was 9.6 months. For details regarding exploratory analysis of subsequent docetaxel therapy, please refer to Section 6.6.6.

6.6.3 Subgroup Analyses

Subgroup analyses of overall survival were conducted based on demographics and baseline characteristics, including prior therapies, disease characteristics, and laboratory values. These subgroups were selected for analysis because of their possible prognostic impact on overall survival. For each subgroup, the HR for treatment effect and the p-value were generated from a Cox regression model with the subgroup as the covariate.

Figure 3: Applicant's Analyses of Subgroups Based on Baseline Covariates.

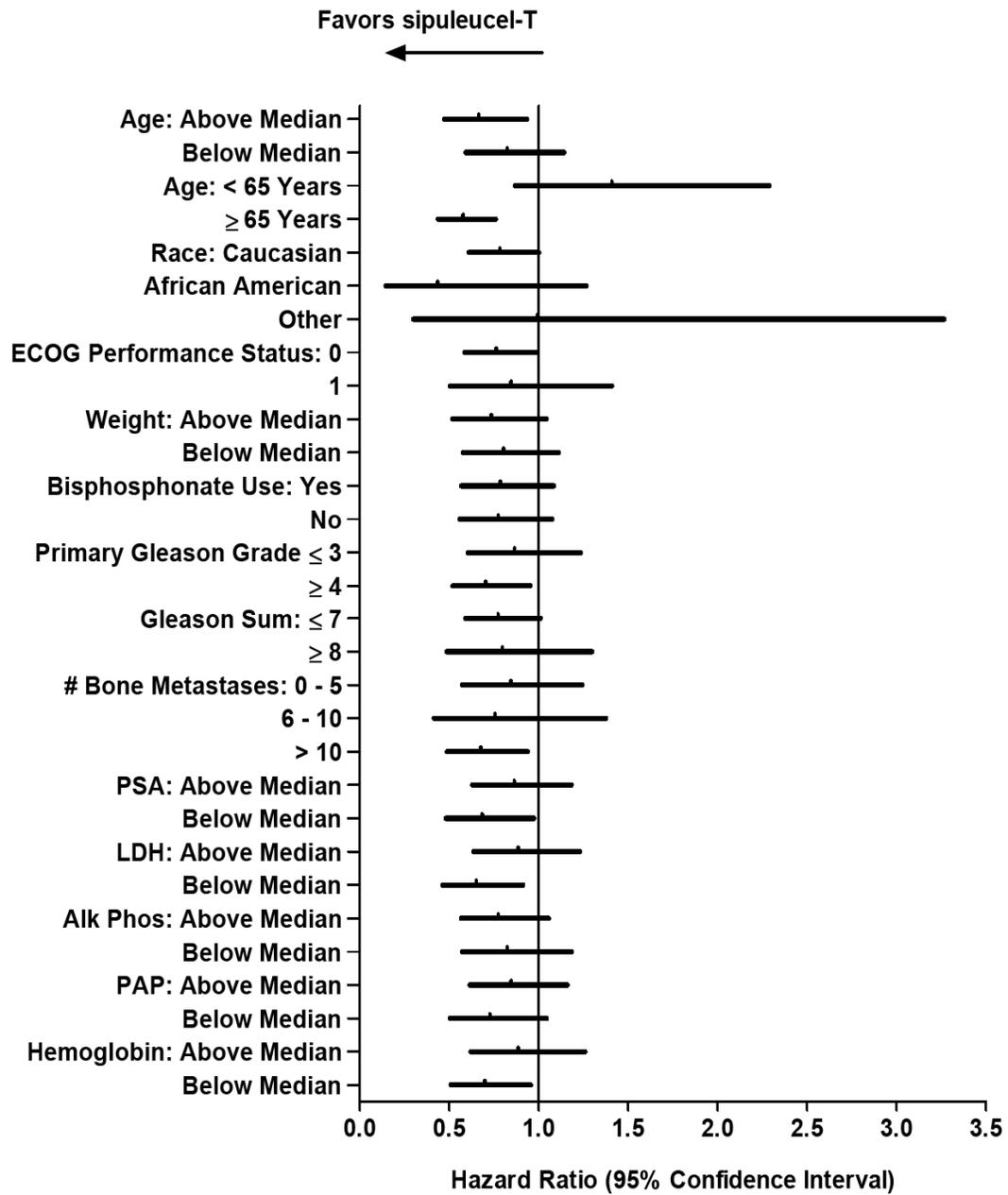
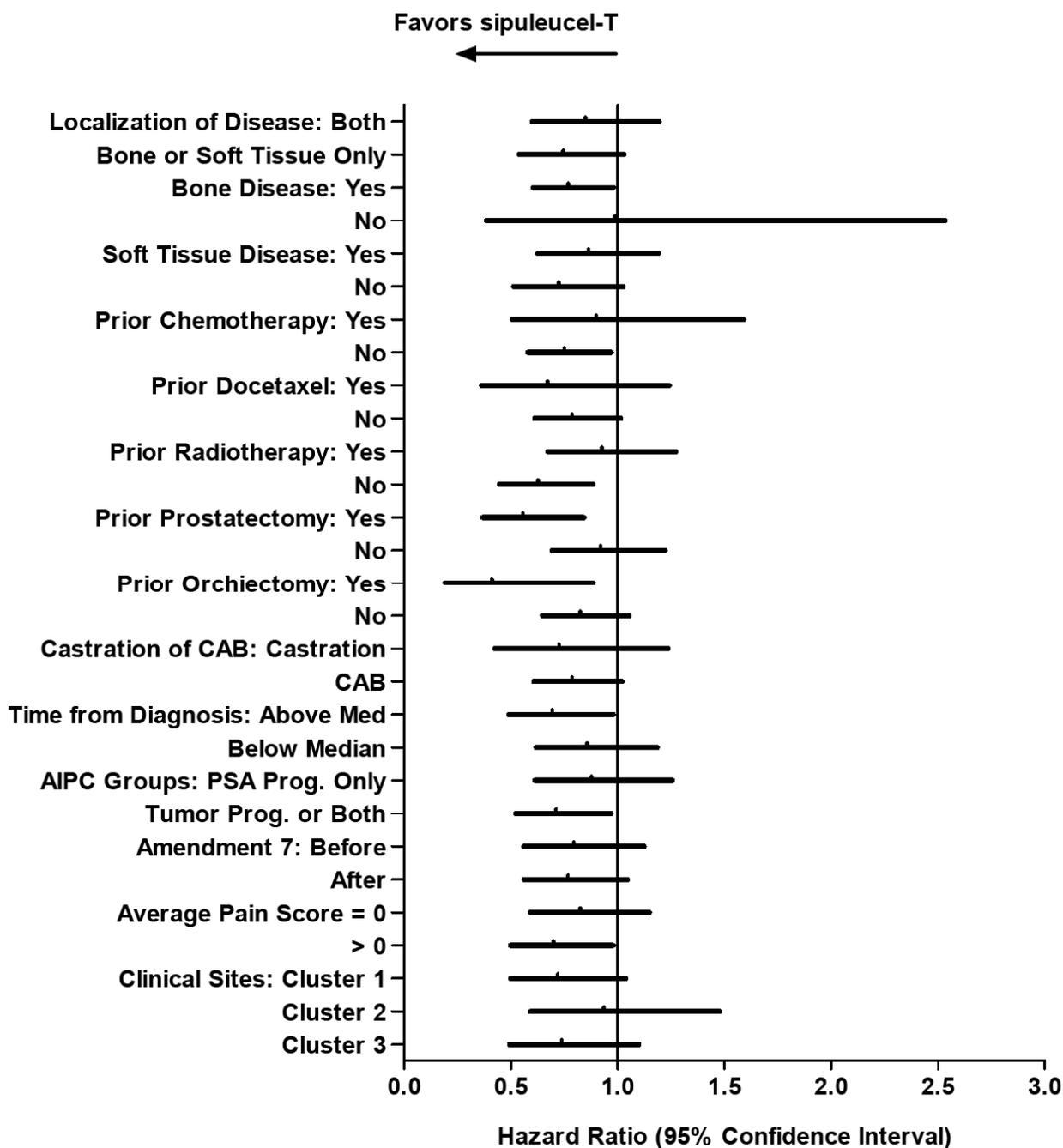


Figure 4: Applicant's Additional Analyses of Subgroup Survival Consistency



Reviewer's comments: The applicant's analyses suggest that an overall survival benefit in favor of sipuleucel-T was consistently observed in most subgroups. The only exception is the subgroup of subjects who were less than 65 years of age. In Study D9902B, there were a total of 126 subjects in the ITT population who were <65 years of age; of these subjects, 77 were in the sipuleucel-T arm and 49 in the placebo arm. In the subgroup of subjects who were less than 65 years of age, the observed hazard ratio of 1.411 (95% CI: 0.869, 2.290) suggests a trend in survival in favor of the control group, compared to the sipuleucel-T group.

To examine the issue of clinical benefit in different age groups, additional exploratory analyses were conducted using the data in D9901 separately, and in all three studies (D9901, D9902A, and D9902B) combined, in subjects who were less than 65 years of age. The FDA statistical reviewer analyzed data combined from all three studies (D9901, D9902A and D9902B) and data from Study D9901 for this age group of < 65 years. These analyses were conducted to further explore the difference in overall survival between sipuleucel-T and control. D9901 was analyzed separately because this study had statistically significant benefit in overall survival, while D9902A did not.

Table 13: FDA Statistical Reviewer’s Analysis of Survival in Subjects < 65 years old

Studies	Sipuleucel-T		Control		Hazard Ratio (Sipuleucel-T vs Placebo)
	N	Median survival in months	N	Median survival in months	
<i>Studies D9901, D9902A and D9902B</i>	106	29 (22.8, 34.2)	66	28.2 (23.4, 32.5)	0.919 (0.618, 1.366)
<i>D9901</i>	13	35.2 (29.7,...)	9	28.2 (23.9, 35.7)	0.445 (0.148, 1.336)

Reviewer’s comments: The exploratory pooled analyses in Table 14 were conducted across multiple studies to analyze the effect of age on the primary endpoint, overall survival. The above analyses of the data from all three studies (D9901, D9902A, and D9902B) support the hypothesis that the subgroup of subjects who were less than 65 years of age also benefit from treatment with sipuleucel-T. The hazard ratio in the subgroup of Study D9902B subjects who were less than 65 years of age most likely resulted from chance, related to the multiplicity of comparisons in 49 different subgroups.

6.6.4 Sensitivity Analyses:

Sensitivity analyses included the following:

1. Sensitivity analysis of overall survival of all death events based on the final analysis plan proposed in the statistical analysis plan.
2. Sensitivity analysis including 5 additional death events that were censored in the primary efficacy analysis but occurred following the data lock date and prior to submission of the CSR.
3. Pre-specified sensitivity analyses of overall survival for baseline covariates, including PSA and LDH.
4. Sensitivity analyses of overall survival were performed to evaluate the effect of major protocol deviations and study conduct issues related to documentation of death.

5. APC8015F Sensitivity Analysis: Sensitivity analyses of overall survival to evaluate the effect of administration of APC8015F to the placebo group after objective disease progression.
6. Docetaxel Sensitivity Analyses: Sensitivity analyses of the effect of subsequent docetaxel treatment, and timing of docetaxel treatment, on overall survival.

Sensitivity analyses 1-4 above all produced p-values of <0.05 , for overall survival, favoring the sipuleucel-T arm over the placebo arm. The statistical reviewer also performed a sensitivity analysis based on the 14 major protocol deviations and using the adjusted death dates based on the verification sources provided by the applicant. The analysis for overall survival was based on the same pre-specified Cox model used for the primary analysis and resulted in a p-value of 0.0324 (Table 18). For details of these sensitivity analyses, please see the statistical review by Boguang Zhen, Ph.D.

Reviewer's comments: The sensitivity analyses suggest that the additional death events, baseline covariates, adjusted death dates, and major protocol deviations did not have a substantial effect on the overall study results, i.e., the improvement in survival associated with sipuleucel-T, compared to control.

6.6.5 APC8015F Sensitivity Analysis.

The applicant conducted a sensitivity analysis of overall survival to evaluate the potential effect of the frozen product APC8015F on the primary efficacy analysis.

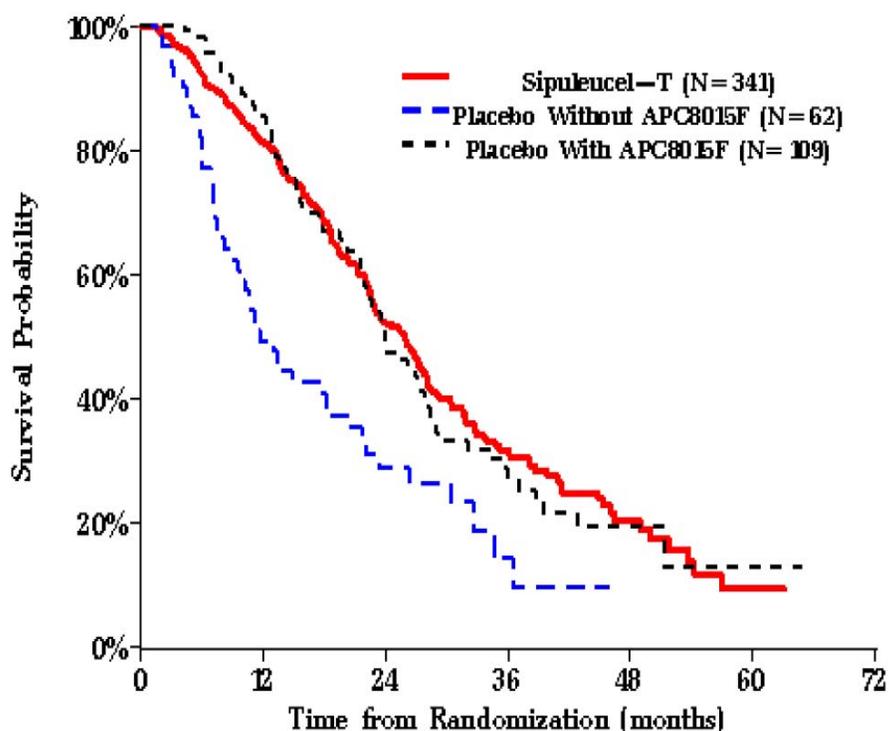
- At the time of independently confirmed objective disease progression, subjects in the placebo arm were unblinded. These unblinded subjects could then choose to receive other anti-cancer interventions, or they could enroll in Study PB-01, an open-label, non-randomized, single-arm study, and receive APC8015F. Eligibility criteria for PB01 included ECOG performance status of <2 , the same laboratory criteria as for entry into D9902B, absence of active infection, and restrictions on concomitant medications (list being the same as for D9902B).
- APC8015F was prepared from the frozen PBMC product that was collected at the time of preparation of the product used as control in the study (APC Placebo). The frozen product was later thawed and pulsed with PA2024 antigen and prepared in a similar manner as sipuleucel-T. Although dosing interval and route of administration were the same as for sipuleucel-T, the preparation of APC8015F differed from sipuleucel-T, in two ways:
 - APC8015F production did not involve PBMCs that were fresh, as in sipuleucel-T, but instead used frozen and thawed PBMCs.
 - For subjects who received sipuleucel-T, the second and third leukaphereses produced PBMCs after the subjects had been exposed to sipuleucel-T in the previous infusion(s). Therefore, subjects who received sipuleucel-T received second and third doses of sipuleucel-T manufactured from blood previously exposed to sipuleucel-T. In contrast, APC8015F was prepared from frozen

PBMCs that were collected and stored at the time of production of APC Placebo (product used in the control). Subjects who received APC8015F received all doses of APC8015F manufactured from blood that had not been previously exposed to APC8015F.

The analysis in Figure 5 was done to explore the hypothesis that APC8015F administration could have affected the results of the primary efficacy analysis. This is a post hoc analysis.

- Of the 171 subjects in the placebo arm, 63.7% (109/171) received APC8015F as part of their subsequent therapy, and 49.1% (84/171) received APC8015F after confirmation of objective disease progression.
- For subjects receiving APC8015F Salvage treatment, the median time from randomization to first infusion with APC8015F was 5.7 months (range: 2.2 – 31.3 months), and median time from objective disease progression to first infusion of APC8015F was 2.7 months (range 0.7 – 14.6 months).

Figure 5: Applicant's Analysis of effects of APC8015F on overall survival



The median survival time for subjects in the sipuleucel-T arm was 25.8 months, for subjects in the control arm who subsequently received APC8015F was 23.8 months, and for subjects in the control arm who did not receive APC8015F was 11.6 months.

Reviewer’s comments: The analysis in Figure 5 was not based on randomized groups; consequently, the groups are not presumed to be comparable at baseline. In addition, the subjects who did not receive APC8015F did not survive as long as expected for minimally symptomatic prostate cancer subjects.¹⁵ This relatively short survival suggests that the difference in survival between the placebo-arm subjects who received APC8015F (23.8 months) and placebo-arm subjects who did not receive APC8015F (11.6 months) is due to selection bias. Considering that the sensitivity analysis presented in Figure 5 is based on non-randomized groups that were likely subject to selection bias, the analysis is insufficient to support any conclusions.

6.6.6 Docetaxel Sensitivity Analyses

The applicant conducted a sensitivity analysis of overall survival to evaluate the effect of non-study anti-cancer interventions on the primary efficacy analysis.

Non-study anti-cancer interventions entered in the Case Report Forms (CRF) included any chemotherapy, docetaxel, hormone therapy, radiation therapy, or surgical intervention received between randomization and long term follow-up. All interventions that occurred after randomization and prior to the data cutoff date were included.

Table 14: Summary of first non-study anti-cancer interventions

Type of Anti-Cancer Intervention	Sipuleucel-T n=341 (%)	Placebo n=171 (%)	Total n=512 (%)
Any anticancer intervention ^a	279 (81.8)	125 (73.1)	404 (78.9)
Docetaxel chemotherapy	195 (57.2)	86 (50.3)	281 (54.9)
Any chemotherapy other than Docetaxel	28 (8.2)	6 (3.5)	34 (6.6)
Hormone therapy except medical castration	42 (12.3)	15 (8.8)	57 (11.1)
Radiation therapy	72 (21.1)	45 (26.3)	117 (22.9)
Surgical Intervention	5 (1.5)	4 (2.3)	9 (1.8)
Other ^b	48 (14.1)	16 (9.4)	64 (12.5)

^a Subjects with multiple anti-cancer interventions were only counted once.

^b Most common types of “Other” anticancer interventions in both treatment groups were investigational therapies, steroid medications, and secondary hormonal therapies.

Median time from randomization to first non-study intervention was 5.4 months (range 0.7- 49.5 months) for the sipuleucel-T arm and 6.2 months (range 1- 36.5 months) for the placebo arm. For subjects in the placebo arm who received APC8015F, the median time to first study intervention was 4.5 months (range 1-36.5 months).

Reviewer’s comments: Subjects in the placebo arm experienced a delay in receiving other anti-cancer therapies, including docetaxel. For all subjects, docetaxel was administered substantially more often than any other non-study intervention. Docetaxel is the only intervention that has been shown to improve survival in metastatic castrate-resistant prostate cancer. Impact of docetaxel salvage therapy was evaluated and is described below.

Docetaxel salvage therapy:

The effect of subsequent docetaxel therapy on the overall survival results of Study D9902B was of concern. Data regarding the total number of cycles of docetaxel and the docetaxel doses were not collected and therefore not available. Exploratory analyses were conducted to evaluate the impact of the following aspects of subsequent docetaxel therapy on the results of the primary efficacy analysis:

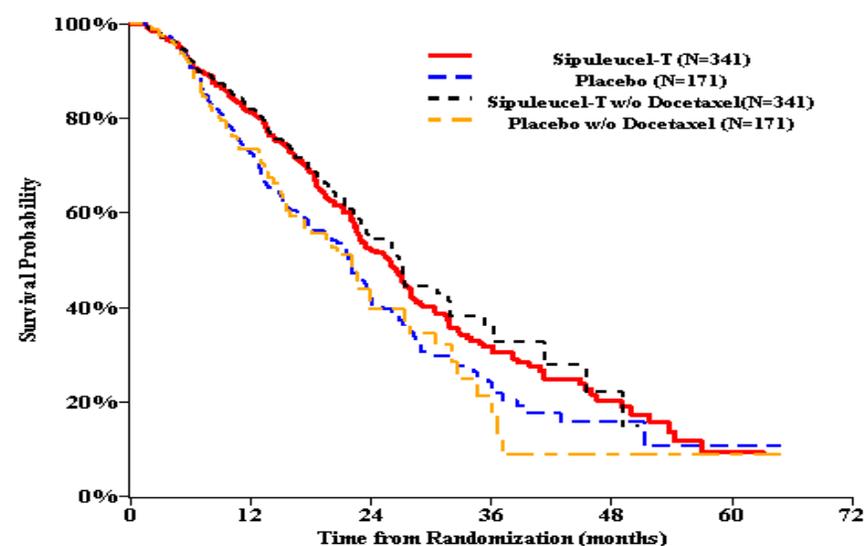
- Censoring for initiation of docetaxel therapy
- Time to docetaxel therapy using specific time periods from time to randomization and initiation of docetaxel therapy
- Interaction of docetaxel therapy with the treatment effect (relative to control) of sipuleucel-T.

An external (to FDA) statistical consult was obtained regarding the effect of docetaxel on the study results. The external statistical consultant endorsed the analyses described above and did not recommend any additional analyses.

Sensitivity analysis of subsequent docetaxel therapy, based on censoring for initiation of docetaxel.

Analysis of the time to docetaxel use was performed for all randomized subjects using the Kaplan-Meier method for overall survival (Figure 7). This analysis used the primary Cox model adjusting for two covariates (log PSA and log LDH) and using the randomization strata. This analysis was done by the applicant to evaluate the effect of sipuleucel-T treatment in the absence of docetaxel. Initiation of docetaxel was considered an event, and subjects were censored for overall survival analysis when docetaxel therapy was initiated.

Figure 6: Applicant's survival sensitivity analysis for docetaxel effect



- Median time from randomization to docetaxel was 7.2 months (range 1.3- 49.5 months) for the sipuleucel-T arm and 9.6 months (range 1- 36.5 months) for the placebo arm, for subjects who received docetaxel.

Reviewer’s comments: This analysis supports the hypothesis that sipuleucel-T had an effect on overall survival. However, this is a sensitivity analysis and is not done to evaluate whether the treatment has an effect on overall survival, but rather to ensure that the results of the primary analysis are robust against different assumptions. The comparison of the two arms is not valid because docetaxel use was not determined by randomization, and was likely heavily influenced by selection bias. In addition there is a censoring bias related to docetaxel use.

Analysis of impact of timing of docetaxel therapy

The analyses in Table 16 were conducted by the FDA statistical review team. The purpose of these analyses was to evaluate a hypothesis that a delay in the time to docetaxel therapy in the placebo group could have had an effect on the primary analysis of overall survival. The groupings of the timing of docetaxel are based on the median time to salvage therapy in all subjects (7.9 months), in the sipuleucel-T group (7.2 months), and in the control group (9.6 months). These analyses using various cut-off times for docetaxel therapy all trend in favor of a survival advantage for sipuleucel-T over control.

Table 15: FDA analyses of the Effect of Timing of Docetaxel therapy

Docetaxel Timing (months)	Sipuleucel-T Median		Placebo Median		Sipuleucel-T vs. placebo Hazard Ratio (95% CI) ²	p-value ²
	N	Survival ¹	N	Survival ¹		
All	195	28.5	86	27.1	0.935 (0.669, 1.307)	0.694
≤ 7.2	97	22.3	32	21.1	0.865 (0.538, 1.390)	0.549
> 7.2	98	44.8	54	35.6	0.768 (0.473, 1.244)	0.283
≤ 7.9	106	22.3	35	21.1	0.808 (0.515, 1.268)	0.353
> 7.9	89	44.8	51	35.6	0.795 (0.477, 1.325)	0.378
≤ 9.6	123	23.1	43	21.5	0.861 (0.568, 1.304)	0.480
> 9.6	72	46.4	43	38.6	0.721 (0.403, 1.290)	0.270
Q1 ³	55	19.2	15	19.9	1.155 (0.577, 2.313)	0.685
Q2	51	25.6	20	21.3	0.563 (0.306, 1.036)	0.065
Q3	43	28.9	26	25.1	0.652 (0.345, 1.235)	0.190
Q4	46	53.7	25	51.2	1.156 (0.475, 2.811)	0.750

¹ Based on a Kaplan-Meier estimate (in months)

² HR and p-value estimated based on Cox model with treatment as independent variable

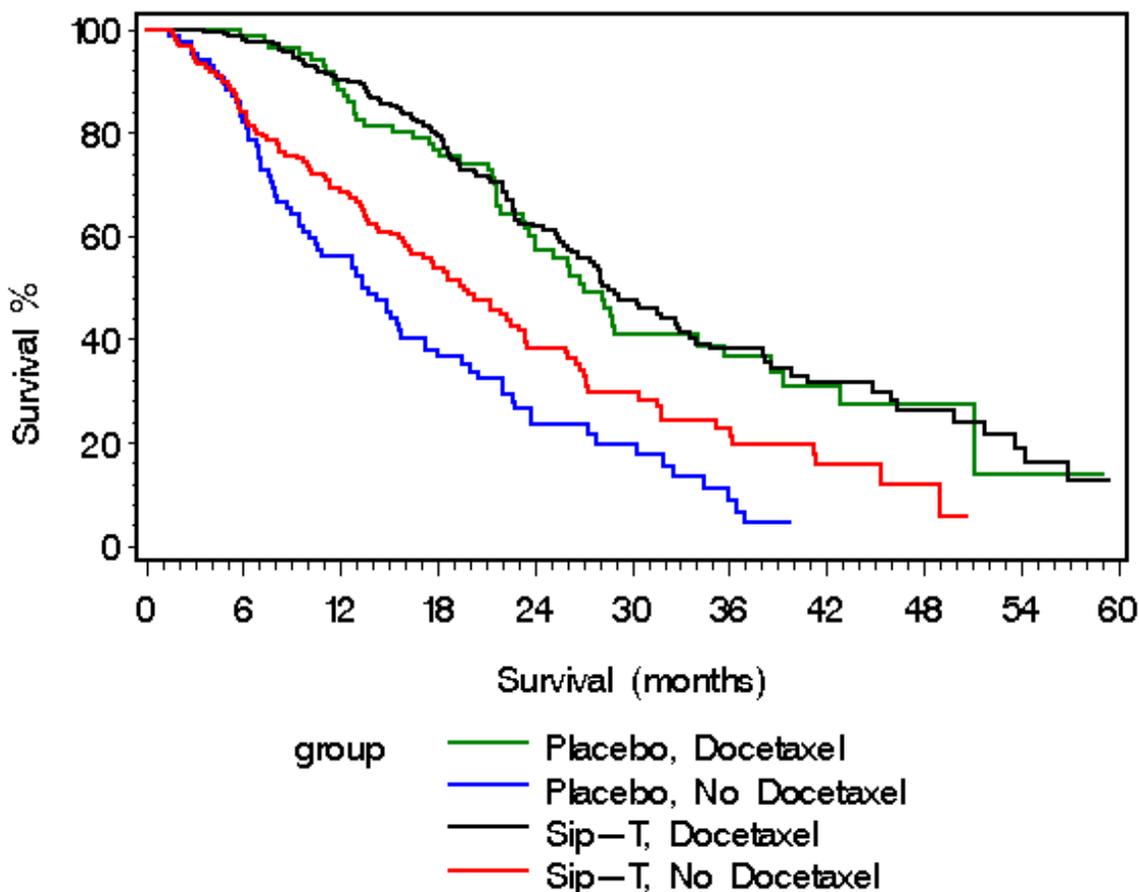
³ Time to docetaxel treatment was divided into four quartile groups: Q1: ≤ 4.5, Q2: >4.5-≤7.86, Q3: >7.86-≤13.38. Q4: >13.38 months.

Reviewer’s comments: This exploratory analysis suggests that the timing of initiation of docetaxel therapy is unlikely to have affected the study’s primary efficacy results.

Docetaxel therapy has a proven survival benefit in metastatic hormone refractory prostate cancer. Therefore, the improvement in overall survival seen in Study D9902B in favor of the sipuleucel-T might be related to the use of docetaxel therapy. To test this hypothesis, a post hoc exploratory analysis

of overall survival was performed to evaluate the interaction of subsequent docetaxel therapy with the treatment effect of sipuleucel-T.

Figure 7: FDA Statistical Reviewer's Sensitivity Analysis by Docetaxel Subgroup



Reviewer's comments: Figure 7 appears to suggest that there was no treatment effect of sipuleucel-T, compared to placebo, in the subgroup that received docetaxel therapy and appears to suggest that there was more of a treatment effect of sipuleucel-T, compared to placebo, in the subgroup that did not receive subsequent docetaxel therapy. However, the median survival (approximately 13.6 months) of the subgroup of placebo-group subjects who did not receive subsequent docetaxel is worse than the expected survival for asymptomatic subjects in historical cohorts who do not receive docetaxel therapy for treatment of metastatic prostate cancer.¹⁵ This relatively short survival suggests a selection bias with regard to the use of subsequent docetaxel therapy. Considering that the above sensitivity analysis is based on non-randomized subgroups that were likely subject to selection bias, the analysis is insufficient to support any conclusions. In addition because of the probability of selection bias, this analysis is not a reliable basis for hypothesis generation.

6.6.7 Analysis of Secondary Endpoint(s)

Time to Objective Disease Progression

- 431 (84.2%) of the 512 randomized subjects experienced a progression event.
- 16 subjects (3.1%) died prior to objective disease progression.
- 4 subjects (0.8%) were censored at the data cut-off date
- 61 subjects (11.9%) discontinued disease progression evaluation without confirmed disease progression prior to the data cut-off date.

Figure 8: Kaplan-Meier Time to Objective Disease Progression in ITT population

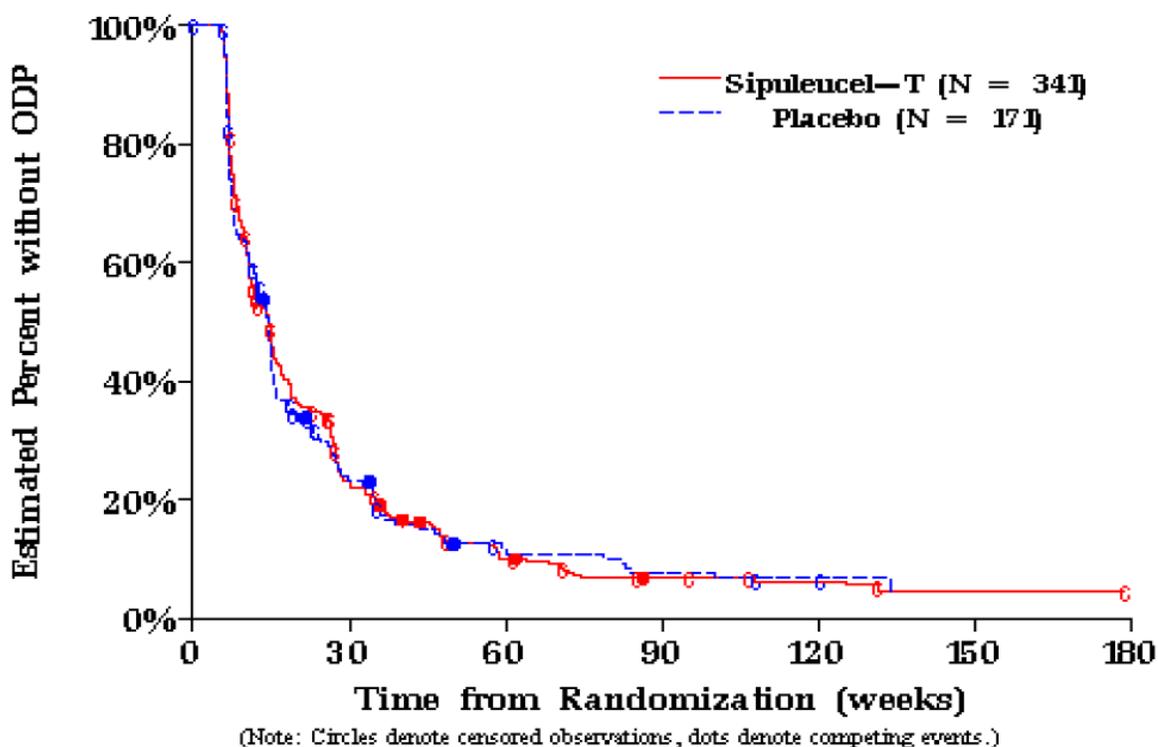


Table 16: Summary of Time to Objective Disease Progression (ITT Population)

Treatment	# of Subjects	# of Events N (%)	HR (95% CI)	p-value
Sipuleucel-T	341	290 (85%)	0.951 (0.773, 1.169)	0.628
Placebo	171	141 (82.5)		

Disease progression events occurred between 5.3 and 131.7 weeks after randomization in the sipuleucel-T arm, and between 5.6 and 133.7 weeks after randomization in the placebo arm.

Reviewer's comments: No significant delay was noted in the time to objective disease progression in the sipuleucel-T arm compared with the control arm. Similar to Study D9902B, Study D9901 did not achieve statistical significance with respect to its primary efficacy endpoint of objective disease progression.

Tumor responses and correlation between overall survival in metastatic prostate cancer:
Metastatic prostate cancer has a strong predilection for systemic bone involvement. In the setting of multiple bony lesions, assessment of progression of individual bone lesions is difficult. Objective tumor progression based on nuclear imaging (the primary modality to establish bone metastasis at baseline) is highly unreliable. The TAX-327 study demonstrated a survival advantage in favor of docetaxel in metastatic hormone refractory prostate cancer; however, the TAX-327 study did not find an improvement in objective tumor response in favor of docetaxel therapy.¹⁷ This lack of correlation between tumor response and survival, as seen in the TAX-327 study and in Study D9902B, may be the result of difficulty in the radiological assessment of metastases to bone and lymph nodes.

6.6.8 Analysis of Tertiary Endpoints

Immune Responses:

Of the 512 subjects randomized, a total of 237 subjects (160 subjects in the sipuleucel-T arm and 77 subjects in the placebo arm) were evaluated for immune responses.

Immune Assays:

Antigen specific humoral responses to PA2024, PAP, and GM-CSF:

Antigen specific humoral responses to PA2024, PAP, and GM-CSF were assessed by Enzyme-linked Immunosorbent Assay (ELISA).

The PA2024 specific responses (antibody titers, both IgG and IgM) were significantly greater than those for PAP or GM-CSF, and were restricted to those subjects who received sipuleucel-T. The anti-PA2024 titer peaked at Week 14 and declined through Week 26. PAP antibody responses were more modest than the anti-PA2024 responses and peaked at Week 14.

Cellular responses to PA2024 and PAP

Cellular responses to PA2024 and PAP were assessed by interferon gamma (IFN- γ) ELISPOT assays and by T cell proliferation assays using ³H-thymidine.

PA2024-specific IFN- γ responses were observed only in the sipuleucel-T group after treatment, with the magnitude of response being greatest at Week 6 (the earliest time-point assayed). No responses were observed for the control subjects. PAP-specific responses were not seen using ELISPOT assays for IFN- γ .

Reviewer's comments: Sipuleucel-T was originally designed to stimulate cellular responses through the PAP antigen; the clinical meaningfulness of the humoral responses, especially

those related to PA2024, is unclear. In summary, both cellular responses and humoral responses to PA2024 and PAP were weak. In addition, the consistent decrease in antibody levels after Week 14 suggests that the humoral response was not persistent. The analytical methods for measuring these responses, including the cellular responses, have not been validated. Therefore, these immune responses are not evidence of efficacy. These results support a conclusion that both humoral and cellular responses can be elicited for a short time following administration of sipuleucel-T; however, these results do not support any conclusion regarding the relationship between any specific immune response and overall survival.

6.6.9 Analysis of Other Endpoints

Progression-Free Survival (PFS)

No significant difference in Progression-Free Survival was observed in the sipuleucel-T arm compared to the placebo arm, based on an HR=0.938 (95% CI: 0.766, 1.149), with a p-value of 0.533 (log rank test).

Reviewer's comments: The result of the PFS analysis is consistent with the lack of difference in objective disease progression. The analysis of PFS was not specified in the statistical analysis plan and is therefore exploratory.

Exploratory Analysis of Cell Product Parameters and Overall Survival

Correlation between each of three key product parameters (i.e., cumulative CD54+ cell count, cumulative total nucleated cell count (TNC), and CD54+ up-regulation (log transformed)), treated as continuous covariates, and overall survival was assessed. The hazard ratios for each of the three parameters (cumulative values based on the sum of values at Weeks 0, 2, and 4) suggested increased survival with increased cumulative CD54⁺ cell count (p=0.016), cumulative TNC (p=0.008), and CD54+ up-regulation (p=0.123).

Reviewer's conclusions: The analysis correlating CD54+ up-regulation with survival is exploratory; therefore, no meaningful clinical conclusions can be drawn. The data presented by the applicant lacks the cut-off values necessary to reliably predict clinical outcomes. In addition, these analyses are difficult to interpret in the absence of baseline CD54+ levels and comparable data from the placebo group.

The applicant's analysis is based on cumulative values of CD54+ up-regulation. However, cumulative values do not permit an ongoing determination of the potential benefit with each dose of treatment. Therefore, cumulative values are not useful in clinical practice. In addition, other factors, such as cumulative TNC, appear to correlate with survival, based on retrospective analysis; therefore, the significance of the analysis of CD54+ up-regulation is unclear. None of these correlations of product parameters and overall survival constitute evidence to support an efficacy claim.

6.6.10 Analysis of Subpopulations:

As noted previously, prostate cancer does not occur in children. Therefore sipuleucel-T was not studied in the pediatric age group.

The pivotal studies did not enroll sufficient numbers of African American, Hispanics or Asians, to permit meaningful analyses by race.

Most of the subjects in the pivotal studies were greater than 65 years of age. In the subgroup analysis, these older subjects appeared to benefit from sipuleucel-T (see Section 6.2.8).

An analysis of the subgroup of subjects who were less than 65 years of age showed no benefit. However, analyses of the other randomized studies (i.e., D9901 and D9902A) did not support this finding.

6.6.11 Analysis of Clinical Information Relevant to Dosing Recommendations

Qualification for potency and minimum requirement for product dose

The number of cells contained within each dose of sipuleucel-T is variable since it depends on numerous manufacturing factors. The minimum number of CD54+ cells that was qualified for potency was 50×10^6 cells. No specific analysis was conducted to evaluate the potential impact of variable doses on the primary efficacy endpoint.

Clinical Development Program and Dose Selection for Phase 3 studies

Early Phase 1 and 2 clinical studies were done in men with castrate resistant prostate cancer (CRPC) to assess the safety and preliminary efficacy of sipuleucel-T. Subjects were treated with a fixed dose of sipuleucel-T administered intravenously on Weeks 0, 4, and 8. For subjects who experienced stable disease or response, an additional dose was administered at Week 24. The Phase 1 study evaluated doses of 0.2×10^9 , 0.6×10^9 , 1.2×10^9 , and 2.0×10^9 nucleated cells/m² and was designed to determine a maximum-tolerated dose (MTD). The upper limit of testing was defined by the anticipated maximum feasible dose of sipuleucel-T. Because a maximum manufacturable dose (MMD; defined as the maximum number of cells that could be produced from a single leukapheresis product) was achieved prior to an MTD, dose escalation was stopped at 1.2×10^9 nucleated cells/m². The results of these trials formed the basis for the dose regimen in the Phase 3 trials. ---b(4)-----

6.6.12 Additional Efficacy Issues and Analyses

Relationship of Timing of infusion to efficacy

The shelf life of sipuleucel-T is 18 hours. To evaluate the effect of increased storage time on efficacy or safety, the FDA requested that the sponsor perform exploratory analyses of the relationship of timing of product infusion to overall survival.

Based on the median time of 14.4 hours, from manufacture to initiation of infusion, the subjects were divided into two groups (i.e., before 14.4 hrs, and after 14.4 hrs). Survival times were similar in these two groups, and the difference in survival between the two groups was not statistically significant.

Additional exploratory analyses used an infusion time of 17 hours as the cut-off to define the two groups (i.e., before 17 hours vs. after 17 hours). The median survival times were 26 months and 24 months respectively. However, the number of subjects (n=24) who received the infusion more than 17 hours after the manufacture of sipuleucel-T was small. Overall, these analyses suggest that the difference in infusion time did not significantly affect survival.

Reviewer's comment: Considering the above analyses, the timing of the sipuleucel-T infusion, prior to the expiration time, is unlikely to affect efficacy in the indicated population.

7 Review of Safety

7.1 Safety Summary

This safety review is based on the safety data from four randomized, placebo-controlled studies (D9901, D9902A, D9902B, and P-11). The review includes integrated safety analyses based on a pooled data set from these four studies. Pooling of the safety data provided a larger data set to explore the safety of sipuleucel-T. This larger data set is particularly useful for the assessment of less common AEs, such as cerebrovascular events.

All 904 subjects (601 sipuleucel-T; 303 placebo) who underwent at least one leukapheresis procedure in these four trials were included in the safety population. The demographic and baseline disease characteristics were fairly balanced between the two treatment groups.

Overall, sipuleucel-T treatment was relatively well tolerated. 841 (93%) subjects received the scheduled three infusions of either sipuleucel-T or placebo. Most subjects developed adverse events during the study, 98.3% in the sipuleucel-T group and 96.0% in the placebo group. Most (67%) subjects had only mild or moderate adverse events, most of which resolved within 48 hours. Chills, fatigue, pyrexia, back pain, and nausea were the most common AEs ($\geq 20\%$ of subjects in the Sipuleucel-T group). These events generally occurred within one day of an infusion with sipuleucel-T, were grade 1 or 2, and were managed on an outpatient basis.

There were fewer deaths in the sipuleucel-T group than in the placebo group, 53% versus 61.7%. Disease progression was the primary cause of death for both treatment groups. Four subjects, three in the sipuleucel-T group and one in the placebo group, died within 30 days after receiving the infusion of the study product, but there was no indication that these deaths were directly related to the infusion of the study product.

Serious Adverse Events (SAEs) other than deaths occurred in fewer subjects in the sipuleucel-T group than in the placebo group (24% versus 25.1%).

Cerebrovascular events (CVEs) occurred in more subjects in the sipuleucel-T group than in the placebo group: 4.0% versus 2.9% (including transient ischemic attacks (TIA)); 3.5% versus 2.6% (excluding TIAs). A slightly higher percentage of subjects in the sipuleucel-T group had fatal outcomes with CVEs, 1.3% versus 0.7% (placebo). However, there were multiple confounding factors which could have contributed to these differences in the incidence of both fatal and total CVEs. The differences were not statistically significant; nevertheless, the increased CVE frequency associated with sipuleucel-T is a safety concern.

7.2 Methods

Safety review materials included the following:

- The applicant's Integrated Summary of Safety (ISS) data sets
- Adverse event tables in the BLA submission (This review determined that adverse event tables provided by the applicant are accurate and fairly represent the data. Applicant-generated tables that are used in this review are identified by source.)
- Case report forms (CRFs) for subjects who died within 30 days after receiving the study product, experienced CVEs, had CVE-associated deaths, experienced serious adverse events, or dropped out of a study because of an adverse event
- Individual subject information, including adverse reaction data listing, laboratory listings, and baseline listings
- The applicant's narrative summaries of deaths, serious adverse events, and other events that resulted in dropouts
- Displays of individual subject safety data over time for subjects who experienced adverse events
- The safety sections of the applicant's proposed labeling

Safety data source materials, including information reported in case report forms, case report tabulations, and narrative summaries for individual patients, were reviewed and compared to assess the consistency of the submitted data. For subjects with important adverse events (e.g., death, serious adverse events, cerebrovascular events, and new primary cancer), the associated CRFs (including hospital record and the submitted laboratory, radiology, and pathology results) were selectively reviewed.

All incidences of adverse events (AEs) in the safety review of this application are subject incidences, unless stated otherwise. A subject was counted only once under the maximum NCI CTCAE grade experienced for each preferred term (PT); i.e., if the same AE occurred on multiple occasions in a subject, the AE with the greatest severity was counted. If two or more different AEs were reported as together temporally, the individual terms were reported as separate events.

Reviewer's comment: The study "placebo" should not be viewed as a true "placebo" from the safety perspective. A true placebo would be expected to have no pharmacologic activity;

for studies that use a true placebo, adverse events that occur with similar incidence in all treatment groups are often attributed to the background disease. However, the non-activated cells that were administered to the subjects in the placebo group in this safety data set could have some pharmacologic activity and be the cause for some incidence of adverse events that should not be viewed as disease background. In addition, subjects in the placebo group underwent leukapheresis procedures, which are expected to produce some incidence of adverse events, such as citrate toxicity. Therefore, comparison of adverse event incidences between the sipuleucel-T group and the placebo group should consider that there was no true placebo in these studies.

7.2.1 Studies/Clinical Trials Used to Evaluate Safety

Clinical data from 904 subjects (sipuleucel-T, N = 601; placebo, N = 303) who participated in the four randomized, placebo-controlled studies (D9902B, D9901, D9902A, and P-11) were reviewed to assess the overall safety profile of sipuleucel-T. The tabular and narrative descriptions of these four studies are presented in review Sections 5.1 and 5.3.

The applicant also submitted summary safety information from ten single-arm, phase 1, phase 2, and compassionate use clinical studies to support the safety of sipuleucel-T. The safety reports of these early-phase studies were reviewed, and there were no unusual safety events that would raise concern. Therefore, this review does not include a detailed analysis and discussion of the safety information from the phase 1, phase 2, and compassionate use studies.

7.2.2 Categorization of Adverse Events

The applicant defined an adverse event (AE) as any undesirable experience concerning the health of a subject that occurred during the clinical trial, including all events, regardless of relationship to study treatment. The nature, severity, and frequency of adverse events, and their relationship to study treatment, were evaluated and scored for severity according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0 and coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 11.0.

A serious adverse event (SAE) was defined as any adverse drug experience that resulted in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization, or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. An important medical event that did not meet these criteria could still have been considered an SAE if, based upon appropriate medical judgment of the investigator, the event could have jeopardized the subject and may have required medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.2.3 Pooling of Data Across Studies/Clinical Trials

Data from four randomized, placebo-controlled studies of sipuleucel-T in subjects with metastatic prostate cancer were pooled to assess the incidences of common and rare adverse events. The four studies included three studies in the proposed indicated patient population of patients with hormone refractory prostate cancer (Studies D99021, D9902A, and D9902) and one study (P-11) in a different population, patients with hormone sensitive prostate cancer.

However, pooling of the four studies is justified only because the four studies were sufficiently similar in design and results. In general, the study designs and patient population are similar for Studies D9901, D9902A, and D9902B. However, Study P-11 enrolled patients with androgen dependent prostate cancer, which is a different population than the proposed indicated population of androgen independent prostate cancer. Other aspects of the P-11 study design, including the randomization ratio (2 sipuleucel-T: 1 placebo), dose, dosing regimen, and route of administration, were similar to Studies D9901, D9902A, and D9902B. In addition, the overall safety profile for Study P-11 is similar to the overall safety profile for the other three studies. These similarities in design and results are sufficient to support pooling of the safety data from Study P-11 with the other three randomized studies to permit an integrated safety review.

Many adverse events associated with the administration of sipuleucel-T appear to be temporally related to the sipuleucel-T infusion. Subjects in all four studies, including Study P-11, completed the study drug infusion and are appropriate for the safety analyses in terms of acute and subacute safety issues related to the sipuleucel-T infusion. Pooling of these four studies increases the safety sample size and permits a more reliable estimate of the incidence of common adverse events. Pooling also facilitates the assessment of rare adverse events, such as cerebrovascular events, a safety signal identified in the review of the original sipuleucel-T BLA submission in 2007.

The primary difference among the four studies was that the patient population in Study P-11 consisted of patients with hormone sensitive prostate cancer. Long term safety data, particularly overall survival, will change for Study P-11 as more information becomes available. However, since Study P-11 did not assess the proposed indicated population, additional long term data is unlikely to alter the overall survival assessment for the proposed indicated patients.

7.2.4 Adequacy of Safety Assessments

The overall clinical data from four randomized, placebo-controlled studies of sipuleucel-T in 904 patients with metastatic prostate cancer is adequate for this safety review. Analyses and discussion of the AE data collection, coding, and transcriptions are provided below.

AE data collection

Due to variations in the protocols, the length of follow-up for collecting AEs varied among the four randomized, placebo-controlled studies included in the safety analyses data set. In Study D9902B, AEs were collected at regularly scheduled study visits, or whenever they occurred, regardless of relationship to study product, until disease progression. Following disease progression, only CVEs, treatment-related AEs, and deaths were collected. In Studies D9901 and D9902A, all AEs were collected through Week 16 (Study Day 112); following Week 16, treatment-related AEs, and deaths were collected for 36 months following randomization. In Study P-11, AEs were collected until the biochemical failure endpoint (see Section 5.3 of this review) was met; after biochemical failure, CVEs, treatment-related AEs, and deaths were collected.

In the four controlled studies included in the safety analyses, adverse event reports were elicited by open-ended questions, appropriately assessed at protocol-specified intervals, and recorded, including severity of the toxicity grade, onset, duration, attribution to the study product, and outcome.

AE data coding and transcription

The integrated safety analyses included all AEs in the D9901 and D9902A databases, all AEs in the D9902B database through the data cut-off of 18 Jan 2009, and all AEs in the P-11 database through the data cut-off of 23 Jan 2009. MedDRA version 11.0 was used to code adverse events for all four studies. Analyses of the overall AE data set were conducted by crosschecking the consistency of the different levels of AE transcription to identify and evaluate AEs with missing information.

In the submitted AE data set, a total of 9767 AEs were listed as treatment emergent (TE) in 883 subjects. A treatment emergent AE was defined as an AE that occurred in a subject who underwent at least one leukapheresis. Three AEs from one subject were excluded from the AE analyses because the subject did not receive a leukapheresis or infusion; therefore, 9764 AEs in 882 subjects were analyzed as the basis for the safety review of this BLA.

All AEs in the safety data set were classified by MedDRA preferred terms. However, system organ classification is missing for 2544 AEs. TE classification is missing for 103 AEs. Further analyses were conducted on these AEs to evaluate the impact of the missing data on the safety review of sipuleucel-T. The results of these analyses are described below.

AEs with missing information on TE classification

There are 103 AEs with missing information for TE classification; those 103 AEs occurred in 8% of subjects in each study group. The majority of AEs with missing TE information were grade 1 and 2. There were no serious adverse events, nor grade 4 or 5 adverse events, among the AEs with missing information on TE classification.

AEs and system organ class (SOC) transcription

All descriptive AEs were transcribed into preferred terms (PT) in all four studies. In Studies D9901, D9902A, and D9902B, all the preferred terms were transcribed into system organ class (SOC). However, in Study P-11, 2544 AEs were not transcribed by SOC. These

unmapped AEs occurred in 22.4% of subjects in the placebo group and 18.9% of subjects in the sipuleucel-T group. Therefore, analyses of adverse events by SOC are limited to data from Studies D9901, D9902A, and D9902B.

Reviewer comments: AEs with missing TE classification occurred in the same percentage of subjects in the two groups; this suggests that there was no systematic bias between groups in the failure to provide TE classification. AEs with missing information on SOC are exclusively from the subjects in Study P-11. A higher percentage of subjects in the placebo group than in the sipuleucel-T group had adverse events that were unmapped by SOC. Therefore, any analyses by SOC may be relatively conservative, in that those analyses might be biased against the sipuleucel-T group. This safety review looked closely at those “uncoded” events, particularly the SAEs, and did not identify any systematic bias regarding which events were not coded. Therefore, the failure to map preferred terms to SOC is unlikely to have a substantial impact on the assessment of the overall safety profile of sipuleucel-T. In summary, the submitted AE data set was adequate for the safety review of this application.

7.2.5 Overall Exposure at Appropriate Doses/Durations

A total of 913 subjects were randomized in Studies D9901, D9902A, D9902B, and P-11; 904 subjects (sipuleucel-T, N = 601; placebo, N = 303) who received at least one leukapheresis were included as the safety population for safety analyses.

7.2.6 Demographics of Target Populations

The following table summarizes the demographics and baseline characteristics of the 904 subjects in the safety analyses population.

Table 17: Demographic and Baseline Characteristics, Safety Database

	Sipuleucel-T N= 601	Placebo N=303
Median age, years (min, max)	70 (47, 91)	69 (40, 89)
Race, Caucasian (%)	89.9	92.1
ECOG Status, 0 (%)	83.1	84.1
Gleason Sum, ≤ 7 (%)	73.9	72.8
Weight, median kg (min, max)	88 (53, 175)	86 (56, 136)
Time from Diagnosis to Randomization, median years (min, max)	6.5 (0.8, 24.5)	6.5 (0.9, 21.5)
Median serum PSA ng/ml (min, max)	33.3 (0.01, 8005.57)	34.07 (0.01, 2799.0)
Median PAP U/L (min, max)	1.90 (0.59, 466.10)	2.40 (0.30, 147.2)
Median LDH U/L	189.50	186.00

(min, max)	(84.0, 173.0)	(101.0, 1662.0)
Median hemoglobin g/dL	13.10	13.2
(min, max)	(5.4, 17.9)	(9.0, 17.0)

Overall, the demographic and baseline disease characteristics were fairly balanced between the treatment groups, sipuleucel-T, and placebo, for the four integrated studies. All subjects were male, and 90.6% were Caucasian. The median age was 70 years (range: 47 to 91 years) in the sipuleucel-T group and 69 years (range: 40 to 89 years) in the placebo group. The majority of subjects from both treatment groups had a baseline ECOG performance status of 0, 83.1% in the sipuleucel-T group and 84.1% in the placebo group. The median time from diagnosis of prostate cancer until randomization was 6.5 years in each group.

Overall Exposure to the Study Products

Leukapheresis was the first step in manufacturing both the treatment and the placebo. The study protocols specified that 3 infusions of sipuleucel-T or placebo were to be administered over a period of 4 weeks. Subjects in Study P-11 were offered an optional booster infusion at the time that biochemical failure was confirmed. Table 19 summarizes the number of subjects who underwent leukapheresis and received infusions of sipuleucel-T or placebo.

Table 18: Summary of leukaphereses and infusion(s), safety population

	Sipuleucel –T N=601 n (%)	Placebo N=303 n (%)
Number of leukaphereses		
1 leukapheresis	9 (1.5)	4 (1.3)
2 leukaphereses	21 (3.5)	6 (2.0)
3 leukaphereses	389 (64.7)	220 (72.6)
4 leukaphereses	148 (24.6)	61 (20.1)
5 or more leukaphereses	34 (5.7)	12 (4.0)
Number of infusions		
0 infusion	12 (2.0)	1 (0.3)
1 infusion	14 (2.3)	7 (2.3)
2 infusions	21 (3.5)	8 (2.6)
3 infusions	554 (92.2)	287 (94.7)
Booster infusions	49 (8.2)	26 (8.0)

As shown in Table 19, there were no substantial differences between the sipuleucel-T and the placebo group in the percentage of subjects who underwent leukaphereses and received the infusions. Of the 904 subjects in the safety population, 841 subjects (93.0%) received ≥ 3 infusions (this includes Study P-11 subjects who may have received a booster infusion).

The majority of the subjects, 92.2% in the sipuleucel-T group and 94.7% in the placebo group, received the protocol-specified three infusions, indicating that the overall exposure of the subjects

to the study product, sipuleucel-T or placebo, is reasonably adequate and balanced for safety review.

Additional exploratory analyses of subject exposure to study product were conducted by three key study product parameters, i.e., total nucleated cell count (TNC), CD54+ cell count, and CD54 upregulation ratio. These three parameters are important for the assessment of product potency and are discussed by Dr. Thomas Finn in the CMC review of this application. The following table summarizes the median cumulative TNC and CD54+ cell counts and CD54+ upregulation ratio per subject in the safety analyses population (Table 20, from applicant’s ISS report).

Table 19: Cumulative Cell Product Parameters Administered in Safety Database

	Sipuleucel –T N=601 Median (range)	Placebo N=303 Median (range)
TNC	9.831 x 10 ⁹ (0.843 x 10 ⁹ to 35.974 x 10 ⁹)	3.384 x 10 ⁹ (0.093 x 10 ⁹ to 8.626 x 10 ⁹)
CD54+	1.877 x 10 ⁹ (0.108 x 10 ⁹ to 8.600 x 10 ⁹)	0.879 x 10 ⁹ (0.003 x 10 ⁹ to 6.988 x 10 ⁹)
CD54+ upregulation Ratio	26.959 (2.900 to 69.648)	2.683 (0.063 to 4.060)

As shown in Table 20, subjects in the sipuleucel-T group received infusions with a higher median cumulative TNC, CD54+ cell count, and CD54 upregulation ratio, compared with subjects in the placebo group. These higher values reflect expected differences between the study product, sipuleucel-T, and the placebo.

7.2.7 Explorations for Dose Response

Each study protocol permitted a wide range in number of CD54+ cells to be infused at each infusion, depending on the availability of the procured and manufactured autologous cells. For example, for Study D9902B, the protocol specified three infusions, each containing the maximum number of cells that could be prepared from a single leukapheresis (minimum 20 x 10⁶ CD54+ cells), given at Weeks 0, 2, and 4; for Studies D9901 and D9902A, the protocol specified that each infusion contain the maximum number of cells that could be prepared from a single leukapheresis (minimum 3 x 10⁶ CD54+ cells) given at Weeks 0, 2, and 4. The Study P-11 protocol specified that each infusion contain the maximum number of cells that could be prepared from a single leukapheresis (minimum 3 x 10⁶ CD54+ cells (prior to Dec 2003); or minimum 20 x 10⁶ CD54+ cells (after Dec 2003)) given at Weeks 0, 2, and 4, and one booster at the time of PSA progression. The cell dose for each infusion was not pre-specified, and there was no limit on the maximum cell dose for each infusion. Therefore, the dose administered to each subject depended on a variety of patient-specific factors and variations in the

manufacturing process. This large variation in dosing makes it difficult to assess the relationship between cell dose and either efficacy or safety. Nevertheless, the effects of infused cell dose on the adverse events are explored and discussed in review Section 7.5.1.

7.2.8 Special Animal and/or In Vitro Testing

Relevant preclinical pharmacology and toxicology studies of sipuleucel-T were submitted to the original BLA (STN 125197.0) in 2007 and were considered sufficient by FDA pharmacology and toxicology reviewers. Based on that review of the original BLA, FDA did not request any additional animal and/or in vitro studies; therefore, no additional pharmacology/toxicology data were included in the current submission.

7.2.9 Routine Clinical Testing

Routine laboratory tests in the clinical trials included complete blood counts (CBCs), serum biochemistries, and urinalyses at every protocol-specified clinic visit. In general, the routine laboratory tests implemented in the clinical studies of sipuleucel-T are considered appropriate and adequate for the study objectives.

7.2.10 Metabolic, Clearance, and Interaction Workup

No data on metabolism and clearance of sipuleucel-T is provided in this submission. Sipuleucel-T is an autologous cell product consisting of a variable number of cells administered intravenously, usually over 30 to 60 minutes. The nature of this product and the highly variable dosing preclude formal pharmacokinetic study and analysis. Therefore, no formal pharmacokinetic data regarding absorption or metabolism of sipuleucel-T were collected during any of the clinical trials of sipuleucel-T.

7.2.11 Evaluation for Potential Adverse Events for Similar Drug Classes

Sipuleucel-T is a first-in-class autologous cellular immunotherapy. Potential adverse events for all cell therapies include infection and malignancy. These adverse events are discussed in the following review Section 7.3.5.

7.3 Major Safety Results

7.3.1 Deaths

Survival was a pre-specified endpoint in the proposed pivotal study (D9902B) submitted to support the efficacy claim of this application. Detailed analyses of the overall survival of the subjects receiving sipuleucel-T and the placebo group are provided in Section 6.1.3 of the efficacy review of this application.

This safety review section provides further analyses of deaths from a safety perspective across all randomized, placebo-controlled studies. To identify any safety signal related to the infusion of sipuleucel-T, this safety review focuses on an analysis of the causes of death, on the deaths that occurred within 30 days following study agent administration, and on deaths within three months after receiving the study agent.

The following table summarizes the death rates from the four randomized studies:

Table 20: Summary of Deaths in the Safety Database

	Sipuleucel-T (N=601) n (%)	Placebo (N=303) n (%)
Number of Subjects who Died prior to Data cut-off	320 (53.2)	187 (61.7)
Study Protocol		
D9901	62 (10.3)	40 (13.2)
D9902A	45 (7.5)	24 (7.9)
D9902B	208 (34.6)	119 (39.3)
P-11	5 (0.8)	4 (1.3)

Overall, as presented in Table 21, fewer deaths occurred in the sipuleucel-T group than in the placebo group, as of the data cut-off date. The majority of deaths occurred in Study D9902B, the proposed pivotal efficacy study. However, in the four randomized, placebo-controlled studies, the death rate was consistently higher in the placebo group than in the sipuleucel-T group.

Causes of Deaths

Causes of deaths for 507 death events from four randomized, placebo-controlled studies were analyzed by the primary causes listed under DCAUSEC in the Death data set. DCAUSEC is a derived variable combining all causes of death provided, and includes deaths listed as “Other or Other Causes of Death” and “Unknown”. Further analyses were performed for the deaths listed as “Other or Other Causes” and “Unknown” by examining comments in another data set (i.e., DCOM) or information from CRFs.

Of note, Study D9902B allowed more than one cause of death to be selected (e.g., disease progression plus other), whereas Studies D9901, D9902A, and P-11 allowed only one cause to be selected. Therefore, some deaths are listed with multiple causes in the data set.

There were 543 deaths listed in the submitted Death data set, including 344 deaths in the sipuleucel-T group and 199 in the placebo group. Among these 543 deaths, there were 537 deaths in the safety population, i.e., subjects who underwent at least one leukapheresis or received at least one product infusion, and six deaths in subjects who did not undergo leukapheresis and were not included in the safety population. Of the 537 deaths in subjects who underwent at least one leukapheresis or received one product infusion, 25 Study D9901 subjects had deaths that were reported after the study closed (with dates of death not

recorded), and five Study D9902B subjects had deaths that were reported after the data cut-off date (January 18, 2009); these 30 deaths were not included in the safety analysis population. Therefore, the safety analysis population contains only 507 deaths.

The following table summarizes the death causes, based on DCAUSEC from the Death data set:

Table 21: Summary of Causes of Deaths in the Safety Database

	Sipuleucel-T N= 601 n (%)	Placebo N=303 n (%)
Number of Subjects who Died prior to Data Cut-off	320 (53.2)	187 (61.7)
Cause of Death*		
Disease Progression	240 (39.9)	151 (49.8)
Infection	2 (0.3)	0
Cardiac Event	5 (1.0)	3 (1.6)
New Primary Cancer	2 (0.3)	2 (0.7)
Cerebrovascular Accident	2 (0.3)	1 (0.5)
Other or Other Cause of Death	48 (8.0)	21 (7.0)
Unknown	20 (3.3)	9 (3.0)
Missing	1 (0.3)	0

*For subjects with more than one cause of death, only the primary cause of death is included in this table.

As seen in Table 22, the majority of deaths were attributed to disease progression, including 240 deaths (39.9% of subjects) in the sipuleucel-T group and 151 deaths (49.8% of subjects) in the placebo group. A higher percentage of subject deaths were attributed to disease progression in the placebo group than in the sipuleucel-T group. “Other or Other Cause of Death”, “Unknown”, or “Missing” was listed as the cause of death for 69 subjects in the sipuleucel-T group and 30 subjects in the placebo group. Further analyses were conducted based on the information from death narratives and CRFs to determine the death causes. Table 23 summarizes the cause of deaths obtained from comments under DCOM and CRFs for subjects listed under “Other or Other Cause of Death”, “Unknown”, or “Missing”.

Table 22: Summary of “Other and Unknown” Causes of Deaths, Safety Database

Number of Subjects who Died prior to Data Cut-off	Sipuleucel-T N=601 n (%)	Placebo N=303 n (%)
Cause of Deaths*: n (%)	69 (11.5)	30 (10.0)
Unknown	47 (7.8)	21 (6.9)
Cerebrovascular Event	6 (1.0)	1 (0.3)
Cerebrovascular accident	2 (0.3)	0
Stroke	3 (0.5)	0
Intracranial bleeding	1 (0.2)	1 (0.3)
Subdural hematoma	3 (0.5)	0

Number of Subjects who Died prior to Data Cut-off	Sipuleucel-T N=601 n (%)	Placebo N=303 n (%)
Brain Aneurysm	1 (0.2)	0
CVA Secondary to Glioblastoma	1 (0.2)	0
Cardiac Event	2 (0.3)	2 (0.7)
Congestive Heart Failure, Myocardial Infarction	1 (0.2)	2 (0.7)
Cardiac Arrest	1 (0.2)	0
Infection	3 (0.5)	1 (0.3)
Urinary Tract Infection	1 (0.2)	0
Sepsis	2 (0.3)	1 (0.3)
Esophageal Carcinoma	1 (0.2)	0
Plasma Cell Leukemia	1 (0.2)	0
Suicide	1 (0.2)	0
Dementia	1 (0.2)	0
Broken leg	1 (0.2)	0
Renal failure	1 (0.2)	0
Severe colitis neutropenia	0	1 (0.3)
Small cell carcinoma	0	1 (0.3)
Respiratory failure	0	1 (0.3)
Aspiration	0	1 (0.3)
Scleroderma	0	1 (0.3)

* per data set DCOM1, for deaths listed as other and unknown in DCAUSEC

Considering all causes of death as shown in Tables 22 and 23, except for deaths resulting from CVA-related events, there is no substantial difference between the sipuleucel-T group and the placebo group in the causes of death. A slightly higher percentage (1.3%) of subjects in the sipuleucel-T group was identified with CVA-related deaths, compared with 0.6% in the placebo group. For a more detailed analysis of the CVA-related deaths, see Section 7.4.5.

Time from initial product infusion to death

To assess the potential relationship of infusion of the study product to deaths, it is important to examine the time when the deaths occurred. The following table summarizes the time of deaths relative to initial product infusion.

Table 23: Time from Initial Product Infusion to Death, Safety Database

	Sipuleucel-T (N=601) n (%)	Placebo (N=303) n (%)
Number of Subjects who Died prior to Data Cut-off	320 (53.2)	187 (61.7)
Time from Initial Product Infusion to Death	Number of Subjects who Died n (%)	
No first Infusion	7 (1.2)	0

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0 - 3 months	9 (1.5)	7 (3.7)
>3 - 6 months	30 (5.0)	16 (5.3)
>6 - 12 months	62 (10.3)	49 (16.2)
>12 - 24 months	119 (19.8)	69 (22.8)
>24 - 36 months	64 (10.6)	40 (13.2)
>36 months	29 (4.8)	6 (2.0)

As shown in Table 24, the majority of deaths occurred more than one year after the initial product infusion.

Seven subjects who died prior to receiving any infusion were all in the sipuleucel-T group; their causes of death were disease progression (four) and unknown (three).

Four deaths occurred within 30 days after receiving the study product infusion, 3 (0.5%) in the sipuleucel-T group and 1 (0.3%) in the placebo group. These four deaths are summarized below.

- Subject 92-057-0712 (sipuleucel-T group), 78 years old, had a medical history of hypercholesterolemia. The subject reported mild transient (duration – ten minutes) slurred speech on the day of the 3rd infusion. He had a stroke two weeks after the 3rd infusion. The subject was unconscious and admitted to hospice care six days post-stroke, and he died ten days post-stroke. No further information is available to determine whether the stroke was ischemic or hemorrhagic. It is unclear whether the subject's slurred speech, presumably a TIA, occurred during the infusion of sipuleucel-T, and whether the subsequent stroke was related to the 3rd infusion. However, the subject had received two previous infusions of sipuleucel-T without event.
- Subject 921230919 (sipuleucel-T group), 75 years old, died 15 days after receiving the 3rd infusion of Sipuleucel-T. The death certificate for this subject was not obtainable and the subject's death was confirmed through the social security index and from telephone conversations with the subject's brother, who informed the applicant that the subject died of disease progression.
- Subject 921640863 (sipuleucel-T group), 82 years old, had a medical history of hypertension and diabetes. He had disease progression measured by CT and bone scans done one day after receiving the 3rd infusion of Sipuleucel-T. The subject died 21 days after the 3rd infusion. The death certificate indicated that the subject died of prostate cancer.
- Subject 921070782 (placebo group), 80 years old, died 30 days after receiving the 3rd infusion of the study product (placebo). The subject had disease progression by CT and bone scans performed four days after the 3rd infusion. Two weeks after receiving the 3rd infusion of the study product, the subject was in hospice care for disease progression and pain management. He died 16 days later.

There is no evidence that deaths within 30 days of infusion were directly associated with the infusion of sipuleucel-T. In addition, all subjects who died within 30 days of receiving the study product were relatively older (range: 75 - 82 years), some with risk of death from other comorbidities. Further analysis of the deaths which occurred within three months after infusion of the study product did not reveal any specific cause of death that was substantially more common in the sipuleucel-T group than in the placebo group. Considering also that death was more common in the placebo group during the first three months after infusion, analysis of the early deaths did not identify a safety issue associated with sipuleucel-T.

7.3.2 Nonfatal Serious Adverse Events

Table 25 summarizes the incidences of SAEs (by preferred terms) that occurred in two or more subjects.

Table 24: Summary of SAEs, by Preferred Term and Treatment group

SAE by Preferred Term	Sipuleucel-T N=601 n (%)	Placebo N=303 n (%)
Any subject reporting SAE	144 (24.0)	76 (25.1)
Cerebrovascular Accident	11 (1.8)	6 (2.0)
Pyrexia	10 (1.7)	1 (0.3)
Spinal Cord Compression	7 (1.2)	2 (0.7)
Chills	6 (1.0)	0
Dehydration	6 (1.0)	4 (1.3)
Dyspnoea	6 (1.0)	1 (0.3)
Atrial Fibrillation	5 (0.8)	4 (1.3)
Transient Ischemic Attack	5 (0.8)	1 (0.3)
Back Pain	4 (0.7)	6 (0.7)
Catheter Sepsis	4 (0.7)	4 (0.4)
Hematuria	4 (0.7)	8 (0.9)
Nausea	4 (0.7)	6 (0.7)
Prostate Cancer Metastatic	4 (0.7)	8 (0.9)
Pulmonary Embolism	4 (0.7)	6 (0.7)
Staphylococcal Bacteraemia	4 (0.7)	0
Anemia	3 (0.5)	2 (0.7)
Arthralgia	3 (0.5)	0
Cardiac Failure Congestive	3 (0.5)	3 (1.0)
Osteoarthritis	3 (0.5)	1 (0.3)
Pneumonia	3 (0.5)	3 (1.0)
Sepsis	3 (0.5)	3 (1.0)
Staphylococcal Sepsis	3 (0.5)	0
Subdural hematoma	3 (0.5)	1 (0.3)
Syncope	3 (0.5)	1 (0.3)

SAE by Preferred Term	Sipuleucel-T N=601 n (%)	Placebo N=303 n (%)
Acute Myocardial Infarction	2 (0.3)	0
Asthenia	2 (0.3)	1 (0.3)
Atrial Flutter	2 (0.3)	0
Bacteraemia	2 (0.3)	1 (0.3)
Brain Mass	2 (0.3)	0
Catheter Bacteraemia	2 (0.3)	0
Cerebral Infarction	2 (0.3)	0
Cervical Vertebral fracture	2 (0.3)	0
Chest Pain	2 (0.3)	0
Chest Wall Pain	2 (0.3)	0
Chronic Myelomonocytic Leukaemia	2 (0.3)	0
Coronary Artery Disease	2 (0.3)	2 (0.7)
Disseminated Intravascular Coagulation	2 (0.3)	1 (0.3)
Gait Disturbance	2 (0.3)	0
Gastrointestinal Hemorrhage	2 (0.3)	0
Hemorrhage Intracranial	2 (0.3)	0
Hyperhidrosis	2 (0.3)	0
Hypertension	2 (0.3)	0
Hypoxia	2 (0.3)	0
Infusion Related Reaction	2 (0.3)	0
Intervertebral Disc Protrusion	2 (0.3)	0
Intestinal Obstruction	2 (0.3)	1 (0.3)
Lacunar Infarction	2 (0.3)	0
Metastasis to Spine	2 (0.3)	0
Muscular weakness	2 (0.3)	1 (0.3)
Myocardial Infarction	2 (0.3)	1 (0.3)
Myocardial Ischemia	2 (0.3)	1 (0.3)
Pain in Extremity	2 (0.3)	0
Pathological Fracture	2 (0.3)	1 (0.3)
Pleural Effusion	2 (0.3)	1 (0.3)
Tachycardia	2 (0.3)	0
Urinary Tract Retention	2 (0.3)	4 (1.3)
Urinary Tract Retention	2 (0.3)	1 (0.3)

Bolded terms are AEs with greater incidence in the sipuleucel-T group than in the placebo group.

Table 26 summarizes incidences by system organ class (SOC) from the four randomized, placebo-controlled studies.

Table 25: Incidence of Serious Adverse Events by System Organ Class

SAE by System Organ Class	Sipuleucel-T N=601 n (%)	Placebo N=303 n (%)
Nervous system disorders	30 (5.0)	6 (2.0)
General disorders and administration site conditions	22 (3.7)	3 (1.0)
Infections and infestations	22 (3.7)	11 (3.6)
Cardiac disorders	17 (2.8)	12 (4.0)
Musculoskeletal and connective tissue disorders	16 (2.7)	4 (1.3)
Respiratory, thoracic and mediastinal disorders	16 (2.7)	6 (2.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	14 (2.3)	9 (3.0)
Gastrointestinal disorders	10 (1.7)	9 (3.0)
Injury, poisoning and procedural complications	10 (1.7)	4 (1.3)
Renal and urinary disorders	10 (1.7)	16 (5.3)
Metabolism and nutrition disorders	9 (1.3)	5 (1.7)
Vascular disorders	8 (0.8)	8 (2.6)
Blood and lymphatic system disorders	5 (0.5)	3 (1.0)
Investigations*	3 (0.5)	2 (0.7)
Skin and subcutaneous tissue disorders	3 (0.5)	0
Eye disorders	2 (0.2)	0
Hepatobiliary disorders	1 (0.2)	1 (1.3)
Missing information**	27 (4.5)	18 (6.0)

Bolded terms are AEs that occurred more often in the sipuleucel-T group than in the placebo group.

* Includes the following preferred terms: white blood cell count increased, transaminases increased, blood creatinine increased, and weight decreased

** AEs mapped by PT, but not by SOC; see discussion in review Section 7.4.1.

Overall, incidences of serious adverse events by preferred terms were balanced between the sipuleucel-T group and the placebo group.

SAEs by preferred terms that occurred in $\geq 1\%$ of subjects and more often in the sipuleucel-T group than the placebo group included pyrexia (1.7% versus 0.3%); spinal cord compression (1.2% versus 0.7%); chills (1.0% versus 0), and dyspnea (1.0% versus 0.3%). Slightly higher incidences of SAEs of pyrexia, chills, and dyspnea in the sipuleucel-T group may reflect the pharmacological effect of sipuleucel-T (activated cells) that was not present in the placebo (non-activated cells). Further review of the cases of spinal cord compression did not identify any safety concerns related to the infusion of sipuleucel-T.

In the analyses of SAEs by system organ class (SOC), differences in the incidences between sipuleucel-T group and placebo group were observed in a few SAEs. SAEs that were at least 1% more frequent in the sipuleucel-T group than in the placebo group included Nervous system disorders (5.0% versus 2.0%); General disorders and administration site conditions (3.7% versus 1.0%); and Musculoskeletal and connective tissue disorders (2.7% versus 1.3%).

- The majority of SAEs in the Nervous System Disorders SOC in both treatment groups were CVEs and transient ischemic attacks (TIAs). Further analyses of these CVEs are in Section 7.4.5.
- SAEs in the General Disorders and Administrative Site Conditions SOC in the sipuleucel-T group included pyrexia in 1.7% (10/601) and chills in 1.0% (6/601) of subjects.
- SAEs in the Musculoskeletal and connective tissue disorders SOC included a variety of preferred terms; no SAEs with a specific preferred term were identified with clearly higher incidence in the sipuleucel-T group.

With the exception of pyrexia and chills, most SAEs occurred more than 14 days after receiving the last study product infusion. In the sipuleucel-T group, the SAEs that occurred within one day of infusion and in more than two subjects included pyrexia in seven subjects (1.2%) and chills in four subjects (0.7%), likely associated with the infusion of the sipuleucel-T, though the number of these SAEs is small.

Reviewer comments: No important differences in the incidence of SAEs were observed between the sipuleucel-T group and the placebo group.

7.3.3 Dropouts and/or Discontinuations

Information about AEs that led to discontinuation of treatment was collected in Study D9902B, but was not systematically collected in Studies D9901, D9902A, and P-11. Therefore, a comprehensive review of the dropouts and discontinuation due to AEs is not possible for the integrated safety population from the four randomized, placebo-controlled studies. However, in Study D9902B few subjects discontinued the study due to AEs. Only 5 of 338 subjects (1.5%) in the sipuleucel-T group did not receive all three infusions because of adverse events. Four (1.2%) of these subjects had infusion-related AEs (hematuria, hypotension, headache, and chills), and one subject (0.3%) had a leukapheresis-related AE (hypotension). No dropouts due to AEs occurred in the placebo group.

Reviewer comment: The dropout rate due to adverse events in subjects receiving sipuleucel-T is low and acceptable.

7.3.4 Significant Adverse Events

The National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) were used to categorize AEs and to score their severity.

The following definitions were provided to investigators to assist in scoring the severity of AEs:

1. Mild: The AE was easily tolerated and did not interfere with normal daily activities.
2. Moderate: The AE produced sufficient discomfort to interfere with some aspects of the subject's activity or required simple treatment.
3. Severe: The AE resulted in discomfort or disability, which incapacitated and prevented most normal daily activities, was clearly damaging to the subject's health, required hospitalization, or complicated treatment.
4. Life-threatening: The AE could have reasonably resulted in death unless immediate medical intervention was undertaken.
5. Fatal.

For analysis of severity, a subject was counted only once under the maximum NCI CTCAE grade experienced for each preferred term (PT). If the same AE occurred on multiple occasions in a subject, the AE with the greatest severity was counted. If two or more different AEs were reported as together temporally, the individual terms were reported as separate events.

The following tables summarize the incidences of Adverse Events by Toxicity Grade and the incidences of grade 3 -5 adverse events that occurred in $\geq 1\%$ of subjects in the sipuleucel-T group, by preferred term and decreasing frequencies.

Table 26: Incidence of Adverse Events by Toxicity Grade

Toxicity Grade	Sipuleucel-T N=601 n (%)	Placebo N=303 n (%)
Total AEs	591 (98.3)	291 (96.0)
Grade 1	137 (22.8)	74 (24.4)
Grade 2	268 (44.6)	120 (39.6)
Grade 3	142 (23.6)	76 (25.1)
Grade 4	24 (4.0)	10 (3.3)
Grade 5	20 (3.3)	11 (3.6)
Ungraded	20 (3.3)	12 (4.0)

Bolded terms are AEs with greater incidence in the sipuleucel-T group than in the placebo group.

Table 27: Incidence of Grade 3 -5 AEs in ≥ 1% of Subjects

Grade 3-5 AEs by Preferred Term	Sipuleucel-T N=601 n (%)	Placebo N=303 n (%)
Any grade 3 -5 AEs	186 (30.9)	97 (32.0)
Back Pain	18 (3.0)	9 (3.0)
Chills	13 (2.2)	0 (0.0)
Anemia	11 (1.8)	7 (2.3)
Arthralgia	11 (1.8)	5 (1.7)
Cerebrovascular Accident	11 (1.8)	6 (2.0)
Dyspnoea	11 (1.8)	3 (1.0)
Spinal Cord Compression	10 (1.7)	1 (0.3)
Pain	7 (1.2)	3 (1.0)
Asthenia	6 (1.0)	2 (0.7)
Fatigue	6 (1.0)	4 (1.3)
Haematuria	6 (1.0)	3 (1.0)
Pyrexia	6 (1.0)	3 (1.0)

Bolded terms are AEs with greater incidence in the sipuleucel-T group than in the placebo group.

Overall, the number of subjects who experienced AEs, for all grades and for each individual grade from 1 to 5, was similar for the two groups. Almost all subjects had at least one adverse event. Most AEs were not severe (grade 1 and 2): 408 (67.4%; sipuleucel-T) versus 194 (64.0%; placebo).

The number of subjects who experienced grade 3-5 (severe, life threatening, and fatal) adverse events was similar in the two groups, 186 (30.9%; sipuleucel-T) versus 97 (32.0%; placebo). In general, grade 3 -5 AEs were balanced between the two groups for most preferred terms. Grade 3 - 5 AEs with a slightly higher incidence in the sipuleucel-T group than in the placebo group included chills, dyspnoea, spinal cord compression, pain, and asthenia. The number of subjects with grade 3 - 5 AEs was small, and the differences in the incidences of these AEs between the two treatment groups were minor.

In summary, no safety concerns were identified in reviewing the most severe AEs (grade 3-5) by NCI CTCAE criteria.

7.3.5 Submission Specific Primary Safety Concerns

The submission includes analyses of the following adverse events of particular interest as potentially associated with the infusion of sipuleucel-T:

- Infections – there are three potential sources of infection:
 - Theoretical increased risk of infection with immunotherapy
 - Venous catheters used for the leukapheresis procedures and administration of infusions

- The preparation, storage, and administration of sipuleucel-T
- Cerebrovascular Events – a previous review (original submission review, 2007) of safety information from Dendreon’s Phase 3 randomized trials (Studies D9902B, D9901, and D9902A) in metastatic CRPC revealed a possible increased incidence of CVEs in subjects randomized to sipuleucel-T compared to placebo.
- New Primary Cancers are a potential concern with an immunotherapy.
- Respiratory Reactions – acute infusion reactions may include pulmonary manifestations such as dyspnea and hypoxia; respiratory reactions are of interest because of their potential serious clinical implications, including the potential need for supportive care.
- Autoimmune Disorders, including respiratory reactions, skin disorders, and renal insufficiency, are a potential concern with an immunotherapy.

Cerebrovascular Events

The 2007 review of safety information submitted to the original BLA (123951.0) identified an increased incidence of CVEs in subjects randomized to sipuleucel-T, compared with subjects randomized to placebo. Therefore, the current review includes exploratory analyses of the cerebrovascular events in the safety data from the four randomized, placebo-controlled studies of sipuleucel-T in subjects with CRPC (D9901, D9902A, D9902B), and hormone dependent prostate cancer (P-11).

CVE incidence in four randomized, placebo-controlled studies

Table 29 summarizes the incidences and characteristics of CVEs from four randomized, placebo-controlled studies (D9901, D9902A, D9902B, and P-11).

Table 28: Summary of Incidence and Characteristics of Cerebrovascular Events

	Sipuleucel –T N=601 n (%)	Placebo N=303 n (%)
CVE incidence	24 (4.0 %)	9 (2.9 %)
Ischemic Stroke	16 (2.7%)	8 (2.6%)
Hemorrhagic Stroke	4 (0.7%)	1 (0.3%)
Unknown stroke	4 (0.7%)	0
TIA *	5 (0.8%)	1 (0.3%)

* TIAs are included in the CVE AE analyses; subjects who had an initial TIA and subsequent stroke were counted under stroke event.

A higher incidence of CVEs including TIA’s occurred in the sipuleucel-T group than in the placebo group, 4.0% versus 2.9 %. The incidence of ischemic strokes was similar between

the two groups. The sipuleucel-T group had a marginally higher incidence of hemorrhagic stroke, unknown type of stroke, and TIA, compared to the placebo group. However, the number of these events was so small that interpretation of the results is difficult.

In summary, a slightly higher incidence of CVEs occurred in the sipuleucel-T group than in the placebo group, 4.0% versus 2.9 % (including the TIA events), and 3.5% versus 2.6% (excluding the TIA events). Neither ischemic nor hemorrhagic stroke was substantially more common in the sipuleucel-T group than in the placebo group.

Analyses of risk factors associated with CVEs

The risk factors potentially associated with CVEs were explored for any imbalance which could have contributed to the difference in CVE incidence between the two groups. The following table summarizes the risk factors for cerebrovascular events in the four randomized, placebo-controlled trials.

Table 29: Summary of Risk Factors of Cerebrovascular Events

Age: median, range**	70 (47-91) years	69 (40-89) years
<70	278 (46.3)	155 (51.2)
70-75	155 (25.8)	70 (23)
76-80	101 (16.8)	47 (15.5)
>80	67 (11.1)	31 (10.2)
CV Risks*	374 (62%)	181 (59%)
Hx of HTN*	22 (3.6%)	9 (3%)
Hx CVA*	10 (1.4%)	3 (0.9%)

* FROM MEDHX data set including, but not limited to, MCONLIT terms CVA, CAD, CARDIAC STENT, CVD- CORONARY BYPASS, HYPERCHOLESTREMIA, HYPERLIPEDEMIA, HYPERTENSION, SMOKER, STROKE, and VASCULAR INSUFFICIENCY

** from BASIC data set

As shown in the Table 30, there are several slight imbalances between the two groups in the percentage of subjects with risk factors for CVEs, all favoring the placebo group. Specifically, the sipuleucel-T group contains higher percentages of subjects ≥ 70 years old, with a history of cerebrovascular risk factors, with a history of hypertension, and with a history of cerebrovascular attack. These slightly higher incidences of CVE risk factors in the sipuleucel-T group may have contributed to the slightly higher rates of CVEs in the sipuleucel-T group.

A history of hypertension may have contributed to the development of CVEs. Of note, 14 out of 24 (58%) subjects in the sipuleucel-T group who had CVEs had a history of hypertension; five out of nine (55%) subjects in the placebo group who had CVEs had a history of hypertension. However, of the 24 subjects in the sipuleucel-T group who developed CVEs, 13 (55%) subjects were ≥ 70 years old, compared with only 3 (33%) subjects ≥ 70 years old with CVEs in the placebo group.

There was no clear difference in the number of days from infusion to CVE events in the sipuleucel-T group (range: 26-1889 days) compared to the placebo group (range: 7 to 1220 days). Only three subjects, two in the sipuleucel-T group and one in the placebo group, developed CVEs within 30 days of infusion.

Deaths associated with CVEs

Further analyses explored the mechanisms (i.e., ischemic, hemorrhagic, or unknown type) of strokes associated with deaths. The following table summarizes the stroke types for the CVE-associated deaths in the four randomized, placebo-controlled trials.

Table 30: Summary of Etiology of CVE-Associated Deaths*

	Sipuleucel –T N=601 n (%)	Placebo N=303 n (%)
CVE Death	8 (1.3)	2 (0.7)
Ischemic stroke	2 (0.3)	2 (0.7)
Hemorrhagic stroke	3 (0.5)	0
Stroke (unknown mechanism)	3 (0.5)	0

* based on information from submitted ISS CVA data sets and CRFs.

Eight subjects in the sipuleucel-T group and two subjects in the placebo group had fatal outcomes from CVEs. Narratives of these deaths are provided in the appendix E.

Reviewer comments:

There were slightly more cases of fatal CVEs in the sipuleucel-T group than in the placebo group, 8/601 (1.3%) versus 2/303 (0.7%). However, considering the subject age group, comorbidities, confounding risk factors for CVEs and deaths, insufficient information to precisely assess the CVE or death causes, and the small number of events, this finding has to be interpreted with caution. In addition, there is insufficient evidence to conclude that a particular type of fatal CVE (i.e., hemorrhagic vs. ischemic) occurred predominantly in the sipuleucel-T group. In summary, it is unclear whether sipuleucel-T administration is associated with an increased risk of CVE-associated death.

Non-neurologic arterial vascular events and non-neurologic venous vascular events

As discussed above, subjects who received sipuleucel-T may have had an increased risk of cerebrovascular events. This finding led to concern that infusion of sipuleucel-T may increase the risk of developing thromboses in patients with prostate cancer. Exploratory analyses of all non-neurologic arterial vascular events and all non-neurologic venous vascular events found no apparent increase in the incidences of non-neurologic arterial or vascular events in the sipuleucel-T group as compared to the placebo group (Tables 37 and 38), as discussed below.

Table 31: Incidence of Non-Neurologic Arterial Events

Preferred Term	Sipuleucel -T N=601 n (%)	Placebo N=303 n (%)
Non-neurologic Arterial Vascular Events	6 (1.0)	2 (0.7)
Myocardial Infarction	3 (0.5)	1 (0.3)
Acute Myocardial Infarction	2 (0.3)	0
Renal Artery Thrombosis	1 (0.2)	0
Embolism	0	1 (0.3)

Table 32: Incidence of Non-Neurologic Venous Events

Non-Neurologic Venous Vascular Events	17 (2.8)	12 (4.0)
Pulmonary Embolism	4 (0.7)	3 (1.0)
Deep Vein Thrombosis	3 (0.5)	6 (2.0)
Catheter Thrombosis	2 (0.3)	0
Jugular Vein Thrombosis	2 (0.3)	0
Vena Cava Thrombosis	2 (0.3)	1 (0.3)
Catheter Related Complication	1 (0.2)	1 (0.3)
Disseminated Intravascular Coagulation	1 (0.2)	0
Mesenteric Vein Thrombosis	1 (0.2)	0
Pelvic Venous Thrombosis	1 (0.2)	1 (0.3)
Thrombosis	1 (0.2)	0
Venous Thrombosis Limb	1 (0.2)	0
Venous Thrombosis	0	1 (0.3)

Non-neurologic arterial vascular events and non-neurologic venous vascular events occurred at similar rates in the two treatment groups.

In addition, the incidence of hemorrhagic events was similar in the sipuleucel-T group and the placebo group: 18.5% versus 17.2%. The incidence of thrombophlebitis was 1.7% in the sipuleucel-T group and 2.6 % in the placebo group.

Reviewer comments:

There is no increased rate of arterial or venous thrombotic events in the sipuleucel-T group compared to the placebo group. Therefore, the difference in the frequency of CVEs does not appear to be a manifestation of a higher risk of all types of peripheral vascular events, particularly thrombotic events, in subjects who received sipuleucel-T.

Reviewer comments on the overall analyses of CVEs:

In summary, there were slightly higher rates of CVEs (4.0% versus 2.9%, including TIAs) and fatal strokes (1.3% versus 0.7%) in the sipuleucel-T group than in the placebo group. However, there is no clear indication that any particular type of stroke (i.e., ischemic versus hemorrhagic) or fatal stroke was preferentially associated with the administration of sipuleucel-T. Considering the underlying disease and other common risk factors for CVEs in the study population, CVE is a serious but uncommon competing comorbidity. The absolute difference of 1.1% between the incidences of CVEs in the two groups was most likely due to random variation. Slight imbalances in the group populations with regard to risk factors for CVEs, favoring the placebo group, may have contributed to the higher CVE incidence in the sipuleucel-T group.

The higher CVE incidence observed in the sipuleucel-T group may be a signal of a true causal relationship between CVEs and the administration of sipuleucel-T. However, an absolute difference of 1.1% in CVE incidence between the two groups is at most a weak safety signal.

Infections

To evaluate the possibility of infection related to the manufacturing and infusion of the study product, the applicant conducted detailed analyses of the overall incidences of infections, infections related to the venous catheters for leukapheresis and infusion procedures, and infections related to the manufacturing process of sipuleucel-T. This reviewer conducted independent review of the overall incidence of infections from the safety data set by preferred terms and system organ class, and reviewed the applicant's findings on the infections related to the venous catheters and the sipuleucel-T manufacturing process. The noteworthy findings are summarized below.

Incidence of infection AEs and SAEs

Overall, the incidences of infections by preferred terms are well balanced between the sipuleucel-T group and the placebo group. Similar percentages of subjects in the two groups developed infection AEs during the course of the study: 165 (27.5%) of subjects in the sipuleucel-T group and 84 (27.7%) of subjects in the placebo group. Similar percentages of subjects in both treatment groups experienced events within one week of their final product infusion, 15.3% of subjects in the sipuleucel-T group compared with 14.5% of subjects in the placebo group. The majority of subjects who developed an infection had an event that was Grade 1 or Grade 2 in severity: 81% of subjects in the sipuleucel-T group and 88.1% of subjects in the placebo group.

A slightly higher percentage of subjects in the sipuleucel-T group than in the placebo group developed an infection AE \geq Grade 3: 30 (5%) versus 10 (3.3%), and a marginally higher percentage of subjects in the sipuleucel-T group than the placebo group had a serious adverse event in SOC infections and infestations: 28 (4.7%) versus 12 (4.0%).

Infections related to the venous catheters used for leukapheresis and infusion procedures

There are limitations on the analyses regarding venous catheters because central venous catheter information was not collected on CRFs for Studies D9901, D9902A, and P-11. In Study D9902B, central venous catheter insertion (yes/no) information was collected, but no dates of insertion or removal were collected. Therefore, the relationship of infection AEs to placement of a central venous catheter, during either the leukapheresis procedure or the study infusion, cannot be reliably determined.

Nevertheless, catheter-related infections were identified in 3.0% (27/904) of subjects in the safety population, 3.2% (19/601) of subjects in the sipuleucel-T group and 2.6% (8/303) of subjects in the placebo group. Therefore, subjects in the sipuleucel-T group did not have a substantially increased rate of catheter-related infections, relative to the placebo group.

Infections related to the manufacturing process of sipuleucel-T

Final sterility results for the study product are not available until -b(4)- days post-infusion. Therefore, a subject could receive study product which was later found to be contaminated.

Three subjects in Study D9902B received study product that was later found to be contaminated. All three subjects had central venous catheters. Two of these subjects experienced adverse events as a result. Subject 92024-1142 experienced a grade 4 SAE of catheter bacteremia following his second infusion; he went on to receive his third infusion of sipuleucel-T without event. Subject 92146-0425 experienced a Grade 2 AE of bacterial infection following his second infusion; he went on to receive his third infusion of placebo after a 1-week delay.

Reviewer comments:

Overall, the incidence of infections was the same (27%) in both groups. However, as discussed in Section 7.0 of this review, the placebo in the studies should not be viewed as a “true placebo” because the subjects in the placebo group underwent leukapheresis and received “non-activated” cell product. The leukapheresis procedures, infusion procedures, and non-activated cells are all expected to be associated with some incidence of adverse events, such as infection, that should not be attributed to the underlying disease process. Therefore, the incidence of infections observed in the placebo group should not be viewed as a “pure” background rate of adverse events; instead, the incidence of infections in each group should be viewed as the total risk of infections related to the study product and procedures.

New Primary Cancers

An immunotherapy might be expected to increase the risk of new cancers. Therefore, a review of AEs from the SOC Neoplasms Benign, Malignant, and Unspecified (Including Cysts and Polyps) was conducted. After excluding events related to metastatic prostate cancer, non-melanoma skin cancers, and benign tumors including meningiomas, a total of 19 subjects reported new primary cancers in Studies D9902B, D9901, D9902A, and P-11, including 14 subjects in the sipuleucel-T group (2.3%) and 5 subjects in the placebo group (1.7%).

Bladder cancer was reported in one subject in each treatment group. Esophageal cancer and chronic myelomonocytic leukemia (CMML) were each reported in two subjects in the sipuleucel-T group. No other new primary cancer events were reported in more than one subject. In the two subjects with CMML, one subject had evidence suggestive of pre-existing CMML, and pre-existing abnormal myelopoiesis could not be ruled out in the other subject.

The median time from the first infusion of the study product to the onset of the new primary malignancies was 359 days for the sipuleucel-T group (range 37 to 1272 days), and 413 days for the placebo group (range 48 to 1496 days). Ten of these new malignancies were fatal, including seven in the sipuleucel-T group (1.2%) and three in the placebo group (1.0%).

Reviewer comments:

In summary, new primary cancers did not develop substantially more often in subjects in the sipuleucel-T group compared with the placebo group. The time to reported onset of these malignancies was also similar in the two groups. Furthermore, the cases of new primary cancers varied in cell type and primary anatomic site. Therefore, sipuleucel-T administration does not appear to be associated with an increased risk for developing any new primary cancer, or for developing any specific category or type of malignancy.

Respiratory Reactions

Respiratory reactions such as dyspnea and hypoxia are pulmonary manifestations of acute infusion reactions, potentially directly related to the infusion of sipuleucel-T. Respiratory reactions are of interest because of their potential serious clinical implications, including the potential need for supportive care.

The applicant conducted analyses of respiratory reaction based on the Asthma/Bronchospasm Standardized MedDRA Queries (SMQ), with the addition of the following preferred terms: hypersensitivity, drug hypersensitivity, dyspnoea, dyspnoea exertional, cyanosis, and oxygen saturation decreased. The key findings are summarized below.

A total of 90 subjects (15.0%) in the sipuleucel-T group and 24 subjects (7.9%) in the placebo group experienced at least one of these respiratory events. The most frequent respiratory AE in the sipuleucel-T group was dyspnoea, which was reported in 8.7% of subjects, compared with 4.6% of subjects in the placebo group.

The incidence of respiratory AEs by time of onset is summarized in the following table replicated from the applicant's ISS Table 26.

Table 33 : Respiratory Adverse Events following Product Infusion

Preferred Term	Sipuleucel-T N=601				Placebo N=303			
	≤ 1 Day	2-3 Days	4-14 Days	>14 Days	≤ 1 Day	2-3 Days	4-14 Days	>14 Days
Any AE	34 (5.7)	3 (0.5)	15 (2.5)	45 (7.5)	2 (0.7)	1 (0.3)	7 (2.3)	16 (5.3)
Dyspnoea	16 (2.7)	3 (0.5)	8 (1.3)	26 (4.3)	1 (0.3)	1 (0.3)	4 (1.3)	10 (3.3)
Hypoxia	5 (0.8)	0 (0.0)	1 (0.3)	2 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Cyanosis	4 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Oxygen Saturation Decreased	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Wheezing	3 (0.5)	0 (0.0)	0 (0.0)	5 (0.8)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Bronchospasm	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Drug Hypersensitivity	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspnea, Exertional	1 (0.2)	0 (0.0)	6 (1.0)	12 (2.0)	1 (0.3)	0 (0.0)	2 (0.7)	6 (2.0)
Hyperventilation	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Allergic Cough	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asthma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypersensitivity	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

More subjects in the sipuleucel-T group than in the placebo group (5.7% versus 0.7%) experienced at least one respiratory AE within one day of infusion. Respiratory events that appeared temporally related to sipuleucel-T (i.e., occurred < 1 day of infusion) included dyspnoea, hypoxia, cyanosis, oxygen saturation decreased, wheezing, and bronchospasm. Dyspnoea was the only respiratory AE that occurred within one day of infusion in >1% of subjects in the sipuleucel-T group.

Events that occurred two or more days after infusion appeared balanced between the treatment groups.

The majority of respiratory events were Grade 1 or Grade 2 (subject incidence of 10.4% in the sipuleucel-T group). Grade 3 events in the sipuleucel-T group included dyspnoea (1.8%), hypoxia (0.5%), cyanosis (0.2%), bronchospasm (0.2%), and drug hypersensitivity (0.2%). The only Grade 3 event in the placebo group was dyspnoea (1.0%). There were no Grade 4 or Grade 5 respiratory events.

Reviewer comments:

A higher rate of respiratory adverse events with an onset ≤ 1 day following infusion was observed in the sipuleucel-T group than in the placebo group. These events appear to be infusion reactions directly related to the administration of sipuleucel-T. Therefore, close monitoring of the patient's respiratory symptoms is recommended during sipuleucel-T infusions.

Autoimmune Disorders

An immunotherapy might be expected to increase the risk of autoimmune disorders. Therefore, the applicant conducted a MedDRA search to identify event terms indicative of potential autoimmune signs, symptoms, or disease states. In addition, a manual review of all event terms for potential autoimmune events was performed.

In Studies D9902B, D9901, D9902A, and P-11, 16.0% (96/601) of subjects in the sipuleucel-T group and 18.2% (55/303) of subjects in the placebo group experienced an event that was captured in this list of potential autoimmune disorder terms. Therefore, these events appeared balanced between treatment arms. No specific type of event occurred in substantially greater frequency in the sipuleucel-T group.

Skin Disorders

An analysis of AEs from the MedDRA SOC of Skin and Subcutaneous Tissue Disorders was conducted by the applicant. The results are summarized below.

In Studies D9902B, D9901, D9902A, and P-11, 21.3% (128/601) of subjects in the sipuleucel-T group and 17.8% (54/303) of subjects in the placebo group experienced an event that was captured in this SOC.

The most common skin disorder was rash, which was reported in 5.2% of subjects in the sipuleucel-T group and 3.3% of subjects in the placebo group. Hyperhidrosis was reported in 5.0% of subjects in the sipuleucel-T group, compared with 1.0% of subjects in the placebo arm. Urticaria was reported in 1.5% of subjects in the sipuleucel-T group and no subjects in the placebo group. Pruritus and night sweats were each reported in approximately 2% of subjects in each treatment group. Other events reported within this SOC were generally rare and had similar incidence rates between the treatment groups.

Reviewer comments:

There appears to be an increased risk of cutaneous events, including rash, urticaria, and hyperhidrosis, associated with sipuleucel-T administration. These events may be cutaneous manifestations of acute infusion reactions.

Renal Insufficiency

An analysis of AEs from the MedDRA SOC of Renal and Urinary Disorders was conducted by the applicant. The key findings are summarized below.

In Studies D9902B, D9901, D9902A, and P-11, 23.8% (143/601) of subjects in the sipuleucel-T group and 24.1% (73/303) of subjects in the placebo group experienced an event that was captured in this SOC. The most common events in both treatment groups were haematuria, dysuria, nocturia, pollakiuria (urinary frequency), hydronephrosis, and urinary retention.

The incidences of specific AEs in this SOC were generally similar in the two treatment groups. However, haematuria was reported in slightly more sipuleucel-T group subjects than placebo group subjects (7.7% vs. 5.9%). Many other AEs in this SOC were reported more often in the placebo subjects, including urinary tract obstruction, hydronephrosis, bladder obstruction, obstructive uropathy, renal failure, and acute renal failure.

Reviewer comments:

No safety signals were identified for renal toxicities associated with the infusion of sipuleucel-T.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Overall incidences and characterizations of common adverse events

This section includes the analyses of the overall incidences and characterizations of adverse events by preferred terms, and AE occurrence in relation to the time after leukapheresis procedures and product infusions.

The following table summarizes the incidence of commonly reported adverse events, defined as AEs reported in $\geq 5\%$ of subjects in both treatment groups, by decreasing frequency in the sipuleucel-T Group:

Table 34: Summary of AEs $\geq 5\%$ Safety population

AE by Preferred Term	Sipuleucel-T N=601 n (%)	Placebo N=303 n (%)
Any subject reporting AE	591 (98.3)	291 (96.0)
Chills	319 (53.1)	33 (10.9)
Fatigue	247 (41.1)	105 (34.7)
Pyrexia	188 (31.3)	29 (9.6)
Back Pain	178 (29.6)	87 (28.7)
Nausea	129 (21.5)	45 (14.9)
Arthralgia	118 (19.6)	62 (20.5)
Headache	109 (18.1)	20 (6.6)
Citrate Toxicity	89 (14.8)	43 (14.2)
Paraesthesia	85 (14.1)	43 (14.2)
Vomiting	80 (13.3)	23 (7.6)
Anemia	75 (12.5)	34 (11.2)
Constipation	74 (12.3)	40 (13.2)
Pain	74 (12.3)	20 (6.6)
Paraesthesia Oral	74 (12.3)	43 (14.2)
Pain in Extremity	73 (12.1)	40 (13.2)

AE by Preferred Term	Sipuleucel-T N=601 n (%)	Placebo N=303 n (%)
Any subject reporting AE	591 (98.3)	291 (96.0)
Dizziness	71 (11.8)	34 (11.2)
Myalgia	71 (11.8)	17 (5.6)
Asthenia	65 (10.8)	20 (6.6)
Diarrhea	60 (10.0)	34 (11.2)
Influenza Like Illness	58 (9.7)	11 (3.6)
Musculoskeletal Pain	54 (9.0)	31 (10.2)
Dyspnea	52 (8.7)	14 (4.6)
Edema Peripheral	50 (8.3)	31 (10.2)
Hot Flush	49 (8.2)	29 (9.6)
Haematuria	46 (7.7)	18 (5.9)
Muscular Spasm	46 (7.7)	17 (5.6)
Hypertension	45 (7.5)	14 (4.6)
Anorexia	39 (6.5)	33 (10.9)
Bone Pain	38 (6.3)	22 (7.3)
Upper Respiratory Tract Infection	38 (6.3)	18 (5.9)
Insomnia	37 (6.2)	22 (7.3)
Musculoskeletal Chest Pain	36 (6.0)	23 (7.6)
Cough	35 (5.8)	17 (5.6)
Neck Pain	34 (5.7)	14 (4.6)
Weight Decreased	34 (5.7)	24 (7.9)
Urinary Track Infection	33 (5.5)	18 (5.9)
Rash	31 (5.2)	10 (3.3)
Hyperhidrosis	30 (5.0)	3 (1.0)
Tremor	30 (5.0)	9 (3.0)
Anxiety	22 (3.7)	18 (5.9)
Depression	22 (3.7)	17 (5.6)
Contusion	16 (2.7)	17 (5.6)

Bolded terms are AEs with greater incidence in the sipuleucel-T group than in the placebo group.

Overall, a slightly higher percentage of subjects in the sipuleucel-T group had adverse events. Adverse events that occurred in $\geq 15\%$ of subjects in the sipuleucel-T group included chills, fatigue, pyrexia, back pain, nausea, arthralgia, and headache.

Nearly all subjects had at least one adverse event during the study. This frequency of adverse events reflects the serious underlying disease, the complex background co-morbidities in the study population, the relatively complex study procedures (i.e., the leukaphereses and infusions), and the risks solely due to the study agents (sipuleucel-T and placebo).

Adverse events occurring \leq 1 day following leukapheresis

Leukapheresis is a pre-requisite procedure for the manufacturing of the study product, and usually occurs 2 to 3 days prior to the infusion of study product. Adverse events that occurred \leq 1 day following a leukapheresis procedure were further evaluated. The following table summarizes the incidence of AEs reported in \geq 5% of subjects in either the sipuleucel-T group or the placebo group, by decreasing frequency in the sipuleucel-T group:

Table 35: Summary of AEs Occurring \leq 1 Day Following a Leukapheresis Procedure

AE by Preferred Term		
Any subject reporting AE	336 (55.9)	164 (54.1)
Citrate Toxicity	86 (14.3)	42 (13.9)
Paraesthesia Oral	71 (11.8)	43 (14.2)
Paraesthesia	67 (11.1)	36 (11.9)
Fatigue	56 (9.3)	19 (6.3)
Chills	33 (5.5)	9 (3.0)
Dizziness	21 (3.5)	15 (5.0)

Bolded terms are AEs with greater incidence in the sipuleucel-T group than the placebo group.

Incidences of adverse events occurring \leq 1 day following a leukapheresis were fairly similar between the sipuleucel-T group and the placebo group (Table 36). The slight differences between the two groups in the incidences of parasthesia oral, fatigue, chills, and dizziness were not considered of clinical significance.

Reviewer comments:

The protocol-specified leukapheresis procedures were identical for the two treatment groups, and the subjects, investigators, and leukapheresis personnel were blinded to treatment assignment. It seems unlikely that previous exposure to sipuleucel-T (e.g., in a previous infusion) would affect the incidence of adverse events associated with a subsequent leukapheresis. In this situation, no difference in the adverse events related to the standard leukapheresis procedures was expected. Therefore, the few differences between the two groups with regard to the frequency of adverse events that occurred \leq 1 day following a leukapheresis are most likely random variations among multiple comparisons, and most likely do not represent increased (or decreased) risks associated with sipuleucel-T.

Adverse events occurring \leq 1 day following infusion of the study product

To characterize the safety profile of sipuleucel-T infusion, adverse events that occurred during or immediately (\leq 1 day) following the infusion of the study product were analyzed. The following table summarizes the AEs that occurred within 1 day following the study product infusion and were reported in \geq 5% of subjects in the sipuleucel-T group and by decreasing frequency in the sipuleucel-T group:

Table 36: Summary of AEs Occurring ≤ 1 Day Following Infusion

AE by Preferred Term	Sipuleucel-T N=601 n (%)	Placebo N=303 n (%)
Any AE	477 (79.4)	148 (48.8)
Chills	300 (49.9)	16 (5.3)
Pyrexia	146 (24.3)	6 (2.0)
Fatigue	126 (21.0)	43 (14.2)
Headache	72 (12.0)	6 (2.0)
Nausea	71 (11.8)	7 (2.3)
Myalgia	47 (7.8)	7 (2.3)
Influenza Like Illness	43 (7.2)	4 (1.3)
Vomiting	42 (7.0)	2 (0.7)
Pain	40 (6.7)	5 (1.7)
Arthralgia	33 (5.5)	10 (3.3)

A higher percentage of subjects in the sipuleucel-T group than in the placebo group reported AEs occurring ≤ 1 day following the infusion of the study product. Specifically, adverse events that occurred ≤ 1 day following the infusion of the study product and were reported in ≥ 20% of subjects in the sipuleucel-T group chills, pyrexia, and fatigue.

Most (95%) of the adverse events occurring ≤ 1 day following the infusion of the study product were mild or moderate in severity (grade 1 and 2); the incidences of grade 3-5 events occurring ≤ 1 day following the infusion of the study product were 6.7% in the sipuleucel-T group and 2.3% in the placebo group. Most of these events resolved in ≤ 2 days.

Adverse events occurring ≤ 14 days following the infusion of the study product

To further characterize the temporal relationship between AE occurrence and the infusion of the study product, adverse events occurring ≤ 14 days following infusion of the study product were evaluated. The following table summarizes the AEs that occurred ≤ 14 days after study product infusion and were reported in ≥ 5% of subjects in either treatment group, by decreasing frequency in the sipuleucel-T group:

Table 37: AEs Occurring in ≤ 14 days Following Infusion of the Study Product

AE by Preferred Term	Sipuleucel-T N=601 n (%)	Placebo N=303 n (%)
Any AE	551 (91.7)	250 (82.3)
Chills	313 (52.1)	24 (7.9)
Fatigue	190 (31.6)	74 (24.4)
Pyrexia	163 (27.1)	16 (5.3)
Nausea	93 (15.5)	18 (5.9)
Headache	92 (15.3)	11 (3.6)
Back Pain	68 (11.3)	42 (13.9)
Arthralgia	59 (9.8)	30 (9.9)
Citrate Toxicity	57 (9.5)	27 (8.9)
Myalgia	57 (9.5)	12 (4.0)
Vomiting	57 (9.5)	11 (3.6)
Pain	55 (9.2)	7 (2.3)
Influenza Like Illness	51 (8.5)	8 (2.6)
Paraesthesia Oral	51 (8.5)	31 (10.2)
Paraesthesia	45 (7.5)	30 (9.9)
Dizziness	40 (6.7)	13 (4.3)
Anemia	37 (6.2)	16 (5.3)
Asthenia	37 (6.2)	8 (2.6)
Diarrhea	33 (5.5)	17 (5.6)
Hypertension	31 (5.2)	3 (1.0)
Pain in Extremity	30 (5.0)	23 (7.6)
Constipation	29 (4.8)	18 (5.9)
Anorexia	23 (3.8)	15 (5.0)
Edema Peripheral	22 (3.7)	15 (5.0)
Musculoskeletal Pain	21 (3.5)	15 (5.0)

The AE profile of sipuleucel-T within 14 day following the infusion of the study product encompasses, and is similar to, the AE profile observed within 1 day following the product infusion. A higher percentage of subjects in the sipuleucel-T group than in the placebo group reported AEs occurring ≤ 14 day following the infusion of the study product. Adverse events that occurred ≤ 14 days following the study product infusion and were observed in ≥ 20% of subjects in the sipuleucel-T group included chills, fatigue, and pyrexia.

Acute Infusion Reactions

Based on the above analyses of common adverse events, it appears that most of the AEs in the sipuleucel-T group and placebo group that occurred shortly after receiving the study product (i.e., within ≤ 1 day) were consistent with AE terms described for acute infusion reactions by NCI CTCAE version 3. Therefore, further analyses of all adverse events consistent with any term included in the NCI CTCAE acute infusion reaction syndrome

were conducted, including evaluations of total, grade 3-5, serious acute infusion reaction AEs, and hospitalizations for acute infusion reaction AEs. The following table summarizes the overall incidence of acute infusion reaction AEs, by decreasing frequency in the sipuleucel-T group.

Table 38: Incidences of NCI CTCAE Acute Infusion Reaction AEs

AE by Preferred Term	Sipuleucel-T N=601 n (%)	Placebo N=303 n (%)
Any AE	428 (71.4)	87 (28.7)
Chills	300 (49.9)	16 (5.3)
Pyrexia	146 (24.3)	6 (2.0)
Fatigue	126 (21.0)	43 (14.2)
Headache	72 (12.0)	6 (2.0)
Nausea	71 (11.8)	7 (2.3)
Myalgia	47 (7.8)	7 (2.3)
Arthralgia	33 (5.5)	10 (3.3)
Hypertension	29 (4.8)	2 (0.7)
Asthenia	28 (4.7)	10 (3.3)
Dizziness	25 (4.2)	6 (2.0)
Hyperhidrosis	21 (3.5)	0
Malaise	17 (2.8)	4 (1.3)
Dyspnea	16 (2.7)	1 (0.3)
Flushing	13 (2.2)	7 (2.3)
Hypotension	11 (1.8)	1 (0.3)
Rash	8 (1.3)	2 (0.7)
Hot Flush	7 (1.2)	4 (1.3)
Lethargy	7 (1.2)	0
Cough	6 (1.0)	3 (1.0)
Hypoxia	5 (0.8)	0
Urticaria	4 (0.7)	0
Feeling Hot	3 (0.5)	0
Tachycardia	3 (0.5)	0
Bronchospasm	2 (0.3)	0
Pruritus	2 (0.3)	2 (0.7)

A higher percentage of subjects in the sipuleucel-T group than in the placebo group developed an acute infusion reaction within 1 day of infusion (Table 39). The most common events that occurred in $\geq 20\%$ of subjects in the sipuleucel-T group were chills, pyrexia, and fatigue. These events also occurred more frequently in the sipuleucel-T group than in the placebo group.

The following tables summarize the incidence of grade 3 acute infusion reaction AEs and hospitalizations due to acute infusion reaction AEs, by preferred term and infusion number:

Table 39: Grade 3 Acute Infusion Reaction Occurring ≤ 1 Day Following Infusion

AE by Preferred Term	Infusion Number		
	1 Sipuleucel-T N=589 n (%)	2 Sipuleucel-T N=575 n (%)	3 Sipuleucel-T N=554 n (%)
Any Grade 3 acute infusion reaction AE	5 (0.8)	12 (2.1)	7 (1.3)
Chills	4 (0.7)	6 (1.0)	3 (0.5)
Bronchospasm	1 (0.2)	0	0
Hypoxia	1 (0.2)	2 (0.3)	0
Nausea	1 (0.2)	1 (0.2)	0
Asthenia	0	0	1 (0.2)
Dizziness	0	2 (0.3)	0
Dyspnea	0	1 (0.2)	0
Fatigue	0	1 (0.2)	3 (0.5)
Headache	0	1 (0.2)	1 (0.2)
Hypertension	0	2 (0.3)	0
Myalgia	0	1 (0.2)	1 (0.2)
Pyrexia	0	1 (0.2)	1 (0.2)
Vomiting	0	1 (0.2)	0

Table 40: Summary of Hospitalizations for Acute Infusion Reactions

AE by Preferred Term	Sipuleucel-T N=601 n (%)	Placebo N=303 n (%)
Any SAE	7 (1.2)	0
Pyrexia	5 (0.8)	0
Chills	4 (0.7)	0
Hypertension	2 (0.3)	0
Hypoxia	2 (0.3)	0
Headache	2 (0.3)	0
Hypertension	1 (0.2)	0
Nausea	1 (0.2)	0

There were 21 subjects in the sipuleucel-T group who had a Grade 3 acute infusion reaction (Table 40). There was no grade 3 acute infusion reaction AE in the placebo group. There was no grade 4 or 5 acute infusion reaction AE in either group.

Seven subjects in the sipuleucel-T group, compared with none in the placebo group, were hospitalized for management of an acute infusion reaction SAE (Table 41).

Three subjects (0.5%) who experienced cardiac arrhythmias within one day of sipuleucel-T infusion. These three events were reviewed and not considered to be manifestations of acute infusion reactions related to the infusion of sipuleucel-T. Narratives of these three cases with cardiac arrhythmia are provided in the Appendix F.

Reviewer comments on the overall common adverse events:

Overall, sipuleucel-T treatment was relatively well tolerated without significant toxicities. Nearly all subjects reported adverse events, 98.3% in the Sipuleucel-T group and 96.0% in the placebo group. However, the majority of these adverse events were mild in severity (grade 1 and 2).

Chills, fatigue, pyrexia, and nausea are the most common adverse events, occurring in \geq 20% subjects in the sipuleucel-T group.

Most adverse events occurred in \leq 14 days following infusion of the study product.

The differences in AE incidences between the sipuleucel-T group and the placebo group are most pronounced for AEs with onset \leq 1 day following the infusion of the study product, 79.4%, in the sipuleucel-T versus 48.8% in the placebo group. Most of the AEs with onset \leq 1 day following the infusion of the study product, were signs and symptoms included in the definition of cytokine release/acute infusion reaction syndrome by CTCAE version 3.0. In summary, AEs with higher incidences in the sipuleucel-T group than the placebo group appear to be mostly acute infusion reactions related to the infusion of sipuleucel-T. The activated cells of sipuleucel-T appear capable of inducing an acute inflammatory reaction in the recipient.

7.4.2 Laboratory Findings

The applicant's analyses and results of the protocol-specified clinical laboratory evaluations were reviewed; no safety signal was identified with significant clinical impact. Except for the measurement of peripheral blood eosinophil counts, there were no consistent discrepancies, either increased or decreased levels, in the laboratory findings, comparing the sipuleucel-T group to the placebo group. A higher percentage of subjects in the sipuleucel-T group had an elevated eosinophil count (eosinophilia) compared with the subjects in the placebo group, 21.8% versus 2.8%; however, the majority of the eosinophilia appeared to be transient and self-limited. The eosinophilia was not clearly associated with an increased rate of clinical infection (see Section 7.3.5). The clinical significance of eosinophilia observed in the sipuleucel-T group is unknown at this time.

7.4.3 Vital Signs

The applicant conducted analyses of vital signs, including blood pressure, temperature, pulse, and respiratory rate, by evaluating the changes from pre-infusion to post-infusion and over time in subjects in the two treatment groups. In summary, there were a small number of subjects in each treatment group who experienced clinically significant changes in vital signs; however, no significant differences were observed between the sipuleucel-T group and the placebo group in the frequency of clinically significant changes. AEs related to hypertension, hypotension, fever, and respiratory reactions were captured in the CRFs and analyzed in the previous review Sections 7.3.2, 7.3.5, and 7.4.1.

7.4.4 Electrocardiograms (ECGs)

No cardiac issues were identified during early development of the product. Baseline ECGs were performed, but ECGs were not required at follow-up in the randomized, placebo-controlled, phase 3 studies. Among the 904 subjects in the safety analyses population, there were only three AEs with cardiac arrhythmias (3 subjects with tachycardia, including 2 subjects with pre-existing atrial fibrillation), and one T wave change reported. There appears to be no increased risk of clinically important cardiac arrhythmias related to the infusion of sipuleucel-T.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies/clinical trials were conducted for the development of this product.

7.4.6 Immunogenicity

The applicant's analyses and reports on the immunological data from Study D9902B are discussed in Section 6.1.3 of this review. Neutralizing antibody responses to GM-CSF were transient. No clinically significant episodes of neutropenia were reported in association with antibodies against GM-CSF. No safety signal was identified in the review of AEs related to autoimmune disorders (see review Section 7.3.5).

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The applicant analyzed the incidence of AEs in relation to the three key cell product parameters (see CMC review by Dr. Thomas Finn) in subjects randomized to sipuleucel-T. The three product parameters evaluated were cumulative CD54+ cell count, total nucleated cell (TNC) count, and CD54 upregulation. The results of those analyses are summarized below.

The applicant defined the following AEs as potential adverse drug reactions (ADRs) to sipuleucel-T: chills, pyrexia, fatigue, headache, nausea, myalgia, influenza-like illness, vomiting, pain, hypertension, asthenia, hyperhidrosis, and dyspnea. These potential ADRs occurred in similar percentages of subjects who received above and below the median cumulative CD54 cell count and TNC count, or in slightly higher percentages of subjects who received above the median.

Further analyses were conducted that were restricted to AEs that occurred on the day of, or the day following, an infusion. Based on this review, there was no association between any of the three product parameters and incidence of the ADRs specified above.

Additional analyses of AEs by NCI Toxicity Grade and cell product parameters in all subjects, and in those subjects who received three infusions, did not reveal any additional safety signals..

Reviewer comments:

The above analyses are exploratory, and subjects were not randomized to these product parameter groupings. Comparison of these groupings may therefore be confounded by differences in subject disease parameters.

7.5.2 Time Dependency for Adverse Events

See Section 7.4.1 regarding analyses of adverse events occurring ≤ 1 day following a leukapheresis procedure, ≤ 1 day following infusion of the study product, and ≤ 14 days following infusion of the study product.

7.5.3 Drug-Demographic Interactions

All study subjects were male; therefore, there is no analysis of an interaction between sipuleucel-T and gender. Only 9.4% of subjects were non-Caucasian; this number was too small to permit a meaningful assessment of the interaction between sipuleucel-T and race or ethnicity.

The applicant conducted analyses of adverse events by age (i.e., < 65 versus ≥ 65 years of age). The major findings are summarized below.

For subjects treated with sipuleucel-T, a similar proportion of subjects < 65 years of age reported AEs, compared to subjects ≥ 65 years of age (97.5% vs. 98.6%, respectively).

For AEs that appear to be potential ADRs to sipuleucel-T (i.e., chills, pyrexia, fatigue, headache, nausea, myalgia, influenza-like illness, vomiting, pain, hypertension, asthenia, hyperhidrosis, and dyspnoea), more subjects treated with sipuleucel-T in the < 65 years of age group reported the following AEs, versus the ≥ 65 years of age group: chills, pyrexia, headache pain, myalgia, influenza-like illness, and hyperhidrosis. However, more subjects

treated with sipuleucel-T in the ≥ 65 years of age group reporting the following AEs, compared to the < 65 years of age group: fatigue, nausea, vomiting, hypertension, asthenia, and dyspnoea. However, none of the differences in the incidence of AEs between subjects of < 65 years of age group and ≥ 65 years of age group were considered to be clinically important.

Overall, the AE profiles in subjects of < 65 years and ≥ 65 years of age group in the sipuleucel-T group appear to be similar.

Reviewer comments:

There is no clear safety signal related to age in subjects receiving sipuleucel-T; older men (≥ 65 years of age) do not appear to be at greater risk for developing AEs than younger men (< 65 years of age).

One limitation of the safety database for clinical studies of sipuleucel-T is the minimal experience in non-Caucasian subjects. Only 52 African American subjects (5.8%) enrolled in the studies. In the United States, African Americans have the highest incidence and mortality rates for prostate cancer. The incidence (per 100,000) is 248.5 for African Americans, compared with 156.7 for Caucasians. The mortality rate (per 100,000) is 59.4 for African Americans, compared with 24.6 for Caucasians (Jemal 2009). Therefore, further studies on the efficacy and the safety of administering sipuleucel-T in African Americans with hormone resistant prostate cancer would be valuable.

The applicant proposed a post-marketing registry study to enroll 1500 subjects, including 200 African American subjects. Such a registry study could provide important information on the efficacy and safety profile of sipuleucel-T in African American subjects with CRPC.

7.5.4 Drug-Disease Interactions

The applicant conducted analyses of AEs in relation to the baseline ECOG performance status of 0 and 1 in sipuleucel-T group subjects. Subjects with an ECOG performance status of 1 did not appear to be at greater risk for developing AEs, compared to subjects with an ECOG performance status of 0.

7.5.5 Drug-Drug Interactions

There have been no reports of drug-drug interactions associated with the administration of sipuleucel-T. However, use of either chemotherapy or immunosuppressive agents (such as systemic corticosteroids) given concomitantly with sipuleucel-T was not permitted in the sipuleucel-T clinical trials. Since sipuleucel-T is designed to stimulate the immune system, use of chemotherapy or other immunosuppressive agents may affect the efficacy and/or safety of sipuleucel-T.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Discussion of the development of new primary cancers in subjects receiving sipuleucel-T is provided under previous review Section 7.3.4.

7.6.2 Human Reproduction and Pregnancy Data

No clinical data on the safety of sipuleucel-T in human reproduction and pregnancy is provided in this submission. The indicated population is exclusively adult male.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable. Prostate cancer is a disease of adult males.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There are no reports of overdose, drug abuse, withdrawal, or rebound effect with sipuleucel-T. Considering that the clinical study protocols did not specify a maximum cell dose for each infusion of sipuleucel-T, the definition of overdose has not been established.

7.7 Additional Submissions / Safety Issues

Following the submission of this BLA 125197.34 on Oct. 30, 2009, the applicant submitted a safety update (BLA 123951.36) on December, 22, 2009, to support the safety of sipuleucel-T in patients with metastatic prostatic cancer.

Specifically, the applicant submitted the safety update for Studies D9902B, PB01, and P-11 that were ongoing as of the data cut-off date for the ISS (18 Jan 2009 for Studies D9902B and PB01, and 23 Jan 2009 for Study P-11). In addition, safety data for Studies P07-1 and P07-2, which were not included in the ISS due to the limited number of enrolled subjects, were also provided.

Review of the applicant's submitted safety update indicates that the safety profile of sipuleucel-T from the safety update reporting period is consistent with the safety profile based on the previous BLA submissions. No new safety signal was identified from the submitted safety update.

8 Postmarket Experience

This product is not currently in commercial distribution. Therefore, there is no postmarketing experience with sipuleucel-T.

9 Appendices

A. Advisory Committee Meeting

On March 29, 2007, FDA held an advisory committee meeting (Cellular, Tissue and Gene Therapies Advisory Committee, supplemented by members of the Oncology Drugs Advisory Committee and several prostate cancer specialists) to seek its advice on the persuasiveness of the sipuleucel T efficacy and safety results initially submitted to the BLA which included results from Studies D9901 and D9902A. In addition, several questions regarding product potency, variability, and mechanism of action were discussed.

After discussions regarding the significance of the CVA's reported in the submitted studies, the committee voted unanimously (17-0) that safety had been established. The Committee recommended that postmarketing pharmacovigilance studies be performed to monitor the incidence of CVA's with attention to the African American population and other minorities.

After additional discussion, the Committee voted 13 yes and 4 no to the question regarding whether there was substantial evidence that the product was efficacious. Despite the nominal majority of yes votes, the majority of Committee members expressed uncertainty regarding treatment effect (increased survival) of sipuleucel T in the intended patient population. In addition, there was a consensus among advisors that the on-going D9902B trial must be completed; that its integrity must not be compromised to confirm the survival difference seen in D9901; and that the under-representation of the African American population should be addressed.

B. Labeling Recommendations

The approved label provides adequate directions for the safe and effective use of sipuleucel-T in the indicated population. The most significant labeling recommendations are summarized below:

- The product was described as containing 50 million autologous CD54+ cells activated with PAP-GM-CSF instead of 50 million activated CD54+ antigen presenting cells.
- PAP-GM-CSF was included in the list of active ingredients.
- Several sections were revised to add or clarify procedures and precautions regarding product receipt, storage, preparation, and infusion.
- The Product Safety Testing subsection was revised to clarify procedures related to product sterility.

- The summary of immune monitoring data was modified to include only significant observations, and to add the statement that no conclusions could be made about the clinical significance of the immune response data.
- The indication statement was limited to the population that was studied in the Phase 3 trials, i.e., men with asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.
- Safety information was provided regarding the incidence of adverse events, severe adverse events, and serious adverse events.
- The control agent was identified as non-activated autologous peripheral blood mononuclear cells.
- The Clinical Trials section of the label was revised to emphasize Study D9902B and de-emphasize Studies D9901 and D9902A. The Patient Counseling Information and Patient Labeling submissions were found to be acceptable.

The Advertising and Promotional Labeling Branch reviewed, and found acceptable, the proposed name for this product. The sponsor will submit the label in Structured Product Labeling format after product licensure.

C. Protocol and Amendments to the Protocol

Study ID and Title:

A Randomized and Double Blind, Placebo-Controlled Phase 3 Trial of Immunotherapy with Autologous Antigen Presenting Cells Loaded with PA2024 (Provenge®, Sipuleucel-T, APC8015) in Men with Metastatic Androgen Independent Prostatic Adenocarcinoma.

Study Objectives

Primary Objective: To assess the safety and efficacy of APC8015 in prolonging survival of men with metastatic androgen independent prostate cancer.

Secondary Objective: To assess the safety and efficacy of APC 8015 in delaying time to objective disease progression in men with metastatic androgen independent prostate cancer.

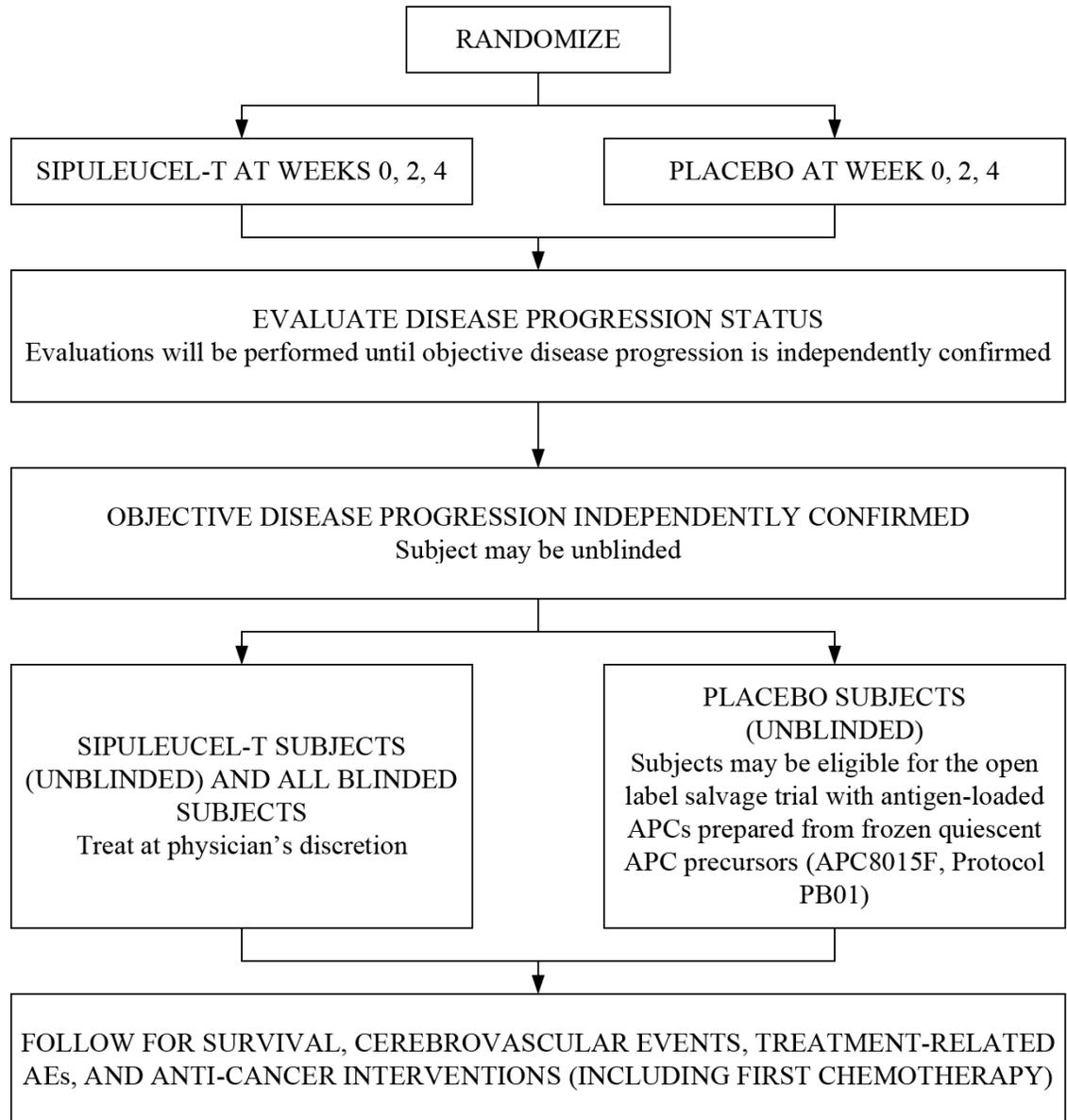
Tertiary Objective: To assess the effect of sipuleucel-T in delaying time to clinical progression, increasing PSADT and generating an immune response.

Study Design

Study D9902B is a randomized, double-blind, placebo-controlled, multi-center study in men with minimally symptomatic or asymptomatic metastatic hormone-refractory prostate cancer. Subjects were randomized in a 2:1 ratio to receive three doses of either APC8015 (sipuleucel-T) or APC-placebo intravenously at Weeks 0, 2, and 4 following determination of eligibility. Subjects who experienced objective disease progression as determined by independent radiology review were unblinded to allow eligible subjects on the placebo arm to cross-over to receive APC8015F under the salvage protocol (PB01). All subjects were allowed to receive additional anti-cancer interventions at the

physician's discretion after independently confirmed objective disease progression. Long term follow-up for each subject was until death.

Overall Schema:



Eligibility Criteria

Inclusion Criteria

- Histologically documented adenocarcinoma of the prostate. Pre-registration submission of specimen for central pathology confirmation of histology and Gleason sum. Exceptions were allowed with applicant's approval if pathology report with clear documentation of primary Gleason Score was provided.

- Evidence of metastatic disease in the soft tissue and/or bone as established by CT scan of the abdomen and pelvis and/or bone scan. Isolated metastatic disease on chest CT alone was ineligible.
- Evidence of disease progression of androgen independent prostate cancer concomitant with surgical or medical castration. Disease progression was evaluated based on any or all of the following parameters:
 - PSA progression: 2 consecutive values at least 14 days apart, each ≥ 5.0 ng/mL and $\geq 50\%$ above the minimum PSA observed during castration therapy or above pre-treatment value if there was no response
 - Progression in measurable disease: $\geq 50\%$ increase in the sum of cross products of all measurable lesions or the development of any new lesions. The change will be measured against the best response to castration therapy or against pre-castration measurements if there was no response.
 - Progression in non-measurable disease:
 - Soft tissue disease: Appearance of ≥ 1 lesion and/or unequivocal worsening of non-measurable disease when compared to imaging studies acquired during castration therapy or against pre-castration studies if there was no response
 - Bone disease: Appearance of ≥ 2 new areas of uptake on bone scan when compared to imaging studies acquired during castration therapy or against pre-castration studies if there was no response.
- Serum PSA of ≥ 5.0 ng/mL
- Castration levels of testosterone of <50 ng/mL. Duration of surgical castration should have occurred at least three months prior to registration, and medical castration should have been initiated at least three months prior to registration and continued until objective disease progression was confirmed.
- Laboratory parameters:
 - White blood cell (WBC) $\geq 2,500$ cells/ μ L
 - Absolute neutrophil count (ANC) $\geq 1,000$ cells/ μ L
 - Platelet Count $\geq 100,000$ cells/ μ L
 - Hemoglobin ≥ 9 g/dL
 - Creatinine: ≤ 2 mg/dL
 - Total Bilirubin ≤ 2 x upper limit of normal (ULN)
 - Aspartate aminotransaminase (AST) ≤ 2.5 x ULN
 - Alanine aminotransaminase (ALT) ≤ 2.5 x ULN

Key Exclusion Criteria

- Liver, lung, or brain metastases, malignant pleural effusions, or malignant ascites.
- Moderately or severely symptomatic metastatic disease as defined by either criterion:
 - Requirement for opioid analgesic within 21 days prior to registration
 - Average weekly pain score ≥ 4 on a 10-point Visual Analog Scale (VAS) on the Registration Pain Log.
- Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2

- Use of non-steroidal anti-androgens (e.g., flutamide, bicalutamide, or nilutamide) within 6 weeks of registration.
- Subjects who demonstrate an antiandrogen withdrawal response, defined as a $\geq 25\%$ drop in PSA following discontinuation of a non-steroidal antiandrogen, are not eligible until the PSA rises above the nadir observed after antiandrogen discontinuation. For verification, subjects on antiandrogens who are being screened for the study should have a PSA obtained shortly prior to antiandrogen discontinuation. Subsequently, a PSA must be obtained = 4 weeks (flutamide) or = 6 weeks (bicalutamide, nilutamide) following antiandrogen discontinuation and prior to registration.
- Chemotherapy treatment within 6 months of registration with the following exception:
 - Chemotherapy treatment ≥ 3 months prior to registration is allowed if all of the following criteria are met:
 - Post-chemotherapy PSA was greater than the pre-chemotherapy PSA or the nadir PSA achieved during chemotherapy.
 - Post-chemotherapy bone scan is not improved in comparison to the pre-chemotherapy bone scan.
 - Post-chemotherapy imaging (CT or other modalities) for subjects with nodal disease must not show a decrease in size or number of pathologically enlarged lymph nodes in comparison to the pre-chemotherapy imaging studies.
 - ≥ 2 Chemotherapy regimens received prior to registration.
 - Initiation or discontinuation of bisphosphonate therapy within 28 days of registration.
 - Subjects on bisphosphonate therapy must not have their dosing regimen altered until objective disease progression is independently confirmed.
 - Treatment with any of the following medications or interventions within 28 days of registration:
 - Systemic steroids
 - External beam radiation therapy or surgery
 - PC-SPES (or PC-SPEC) or saw palmetto
 - Megesterol acetate, diethylstilbestrol (DES), cyproterone acetate, ketoconazole, 5 alpha-reductase inhibitors (e.g., finasteride, dutasteride)
 - High dose calcitriol ($>7 \mu\text{g}/\text{week}$)
 - Any other systemic therapy or any other investigational product for prostate cancer.
 - Treatment with any investigational vaccine within two years of registration or treatment with any other investigational product within 28 days of registration.
 - Participation in any previous study involving sipuleucel-T, regardless whether the subject received sipuleucel-T or placebo.
 - Pathologic long-bone fractures, imminent pathologic long-bone fracture (cortical erosion on radiography $> 50\%$) or spinal cord compression.

- Paget's disease of bone
- Stage III or greater cancer, excluding prostate cancer.
- Basal or squamous cell skin cancers must have been adequately treated and the subject must be disease-free at the time of registration. Subjects with a history of stage I or II cancer must have been adequately treated and been disease-free for ≥ 3 years at the time of registration.
- A requirement for systemic immunosuppressive therapy for any reason.
- Any infection requiring parenteral antibiotic therapy or causing fever (temperature $> 100.5^{\circ}\text{F}$ or 38.1°C) within one week prior to registration.
- A known allergy, intolerance, or medical contraindication to receiving the contrast dye required for the protocol-specified CT imaging.
- Any medical intervention or other condition which, in the opinion of the Principal Investigator or the applicant Medical Monitor, could compromise adherence with study requirements or otherwise compromise the study's objectives.

Treatment Plan

Pre-registration

Pre-registration is to be done after obtaining written informed consent. Study coordinator will receive confirmation along with unique subject number, following which the evaluations listed below must be completed to establish subject eligibility. Imaging studies must be obtained as outlined in the Imaging Manual.

- Adenocarcinoma of the prostate must be confirmed and Gleason Sum must be re-graded by central pathology lab and must be received at least two or more days prior to registration.
- ECG within 28 days of registration
- Medical history, physical exam, ECOG assessment, pain assessment, laboratory tests and immune monitoring blood sample must be obtained within 28 days of registration.
- CT chest and CT of the abdomen and pelvis performed within 14 days prior to registration
- Bone scan with number of bone lesions quantified and categorized within 14 days prior to registration.
- Registration pain log completed within 14 days prior to registration.

Scheduling of subjects with the leukapheresis center and manufacturing facility will be done by applicant's Manufacturing Coordinator after the necessary screening procedures are completed.

Schedule of Events (time scale in weeks)

	Baseline	0	2	4	6	10	14	18	22	26	30	34	Q4	Q12	Long Follow-up (2 months Q6)
Pathology (Gleason Sum)	X														
Leukapheresis & Infusion		X	X	X											
Clinical															
History and Physical Exam ^a	X		X	X	X		X			X		X		X	
Telephone Assessment ^b						X		X	X		X		X		
Registration Pain Log	X														
Survival follow-up															
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	
Electrocardiogram	X														
Staging^c															
CT of Chest	X														
Bone Scan (Full Body)	X				X	X	X	X	X	X		X		X	
CT of Abdomen and Pelvis	X				X		X			X		X		X	
Laboratory Tests															
HIV 1 & 2, Hepatitis B, Hepatitis C, HTLV-1	X														
Testosterone	X						X								
Serum PAP	X						X					X			
PSA	X				X		X			X		X		X	
CBC & Differential	X				X		X			X		X		X	
Bun / Creatinine	X				X		X			X		X		X	
Na ⁺ , K ⁺ , Ca ⁺⁺ , Mg ⁺⁺	X				X		X			X		X		X	
LFTs: Total bilirubin, AST, ALT, Alkaline Phosphatase	X				X		X			X		X		X	
LDH	X				X		X			X		X		X	
Albumin, Total Protein	X				X		X			X		X		X	
Urinalysis	X				X		X			X		X		X	
Immune Monitoring	X				X		X			X					

Secondary endpoint met as verified by IRRC; Subject may be unblinded^d

^aA full history and physical exam, including ECOG and pain assessments, must be performed at baseline. At subsequent time points, a problem-oriented history and physical exam with ECOG are required.
^bEvaluate AEs. A clinical evaluation should be scheduled if indicated.
^cAll imaging studies must be performed using the techniques described in the Imaging Manual. Subjects who meet initial criteria for a CR or PR must be restaged ≥ 4 weeks later to confirm the response.
^dCan occur at any point in active follow-up. After confirming the objective disease progression endpoint, subjects continue long term follow-up.
^eAfter the subject has independently confirmed objective disease progression, only treatment related AEs should be reported.
^fIf the subject has demonstrated independently confirmed objective disease progression prior to the Week 26 visit, a sample for immune monitoring should be obtained at the study visit 2 months after objective disease progression.

Registration and Randomization

- Registration and randomization is to be done one business day prior to the first leukapheresis, with exceptions up to three business days in certain circumstances after applicant approval.

- If subject eligibility criteria are met, applicant will register and randomize the subject to receive APC8015 or APC-Placebo in a 2:1 ratio. For subjects who are not eligible, the clinical sites will be informed and leukapheresis will be cancelled.

Leukapheresis and infusions

Leukapheresis will be done on Weeks 0, 2, and 4 and cells transported to the manufacturing facility for manufacturing of either APC8015 or APC-Placebo. The cell product is released 2-3 days after leukapheresis for infusion of APC8015 or APC-Placebo to the subjects. The Quality Control (QC) testing of the cell product is conducted in parallel with the transport of the cell product to the clinical research center. Infusion of the cell product is to be done only after the QC testing is completed and the Cell Product Disposition Form marked “approved” is faxed to the study center.

Infusion procedure:

- 30 minutes prior to infusion, subjects must be pre-medicated with 650mg of acetaminophen and 50mg of diphenhydramine.
- Infusion of the cell product must begin prior to the labeled expiration time and maintained in the refrigerated shipping package or stored at 2-8°C until infusion.
- Infusion is done over 60 minutes through a large bore IV line suitable for blood transfusion, without the use of a filter.
- Infusion rates may be modified for subsequent infusions if the subject experiences pyrexia and/or rigors, with duration of infusion adjusted to the shortest period that it is tolerated, but not less than 60 minutes.
- Post-infusion follow-up is 30 minutes.
- History and Physical exam will be conducted to evaluate the subject’s tolerability for leukapheresis seven days prior to the second and third procedures.

Ancillary Therapy:

- When appropriate, subjects must receive full supportive care, including transfusions of blood and blood products, antiemetics, and antibiotics.
- The treatments, dosages, reasons, and dates of treatment should be recorded in the CRF.
- Subjects on Lutenizing Hormone-Releasing Hormone (LHRH) agonist or other medical castration therapy at registration must continue on therapy.
- Subjects requiring other supportive medications or initiating medications for newly developed conditions while on the study that may affect study endpoints must be discussed with the applicant’s Study Monitor or designee to ensure that study outcomes will not be interfered with.

Subjects who require systemic therapy for prostate cancer prior to objective disease progression (but based on clinically significant disease specific events or rapidly rising PSA) should remain on study and continue their evaluations for objective disease progression. Therapeutic interventions of this nature must be

discussed with the applicant's Medical Monitor prior to initiating ancillary therapy. These subjects will not be un-blinded until objective disease progression.

- Treatment and Unblinding Following Independent Confirmation of Objective Disease Progression
 - Following independent confirmation of objective disease progression, subjects may be unblinded to determine treatment assignment.
 - Subjects who received placebo have the option of receiving APC8015F under salvage protocol PB01.
 - Unblinding and participation in PB01 is not allowed for those subjects who discontinue study prior to independently confirmed objective disease progression.

Treatment Modifications

Criteria for stopping infusion of investigational product prior to planned three infusions:

- \geq Grade 4 toxicity¹ (unacceptable toxicity)
- Subject's decision
- Inability to manufacture sipuleucel-T or placebo that will pass quality checks

Efficacy Assessment

Active assessment:

- Restaging Bone Scans will be performed 6 weeks after the first infusion and at Weeks 10, 14, 18, 22, 26, and 34.
- Restaging CT scans will be performed at Weeks 6, 14, 26, and 34
- Evaluation for clinical progression at the time of scheduled study clinic visits at Weeks 2, 4, 6, 14, 26, and 34 or as clinically indicated
- Serum PAP will be repeated at Weeks 14 and 34
- Serum PSA will be tested at baseline and Weeks 6, 14, 26, and 34 and every 12 weeks thereafter until objective disease progression.
- Immune-monitoring blood samples will be drawn at baseline and at Weeks 6, 14, and 26 until objective disease progression. For subjects who progress prior to objective disease progression, immune-monitoring samples will be drawn two months following objective disease progression.
- Evaluations for clinical progression (or as clinically indicated), bone scans, and CT scans will be obtained every 12 weeks after Week 34.
- Evaluations for clinical progression and imaging studies are no longer required when objective disease progression is independently confirmed.
- Confirmation of Complete Response (CR) or Partial Response (PR) by imaging studies will be repeated \geq 4 weeks later to confirm the response.
- For additional details please refer to Table 1.

¹ NCI Common Toxicity Criteria for Adverse Events

Criteria for evaluation of Clinical Endpoints:

Baseline and all subsequent bone scans and CTs must be obtained according to the procedure outlined in the Imaging Manual.

Measurable Disease: Soft tissue lesions with clear borders that can be accurately measured on CT or magnetic resonance (MR)†† with 2 diameters ≥ 2.0 cm. The prostate may not be a site of measurable disease; however, pelvic lesions outside the prostatic fossa may be evaluated as measurable.

Non-Measurable Disease: All other soft tissue lesions, including small lesions (at least one diameter < 2.0 cm on CT or MR), leptomeningeal disease, ascites, pleural or pericardial effusion, lymphangitis cutis/ pulmonis, cystic lesions, and cervical nodes. The prostate may not be a site of non-measurable disease; however, pelvic lesions outside the prostatic fossa may be evaluated as non-measurable. All bone lesions, as noted on full body bone scan. Skeletal events, such as pathologic fracture or skeletal-related spinal cord compression, will be considered non-measurable.

Index Lesions:

- Will be chosen at baseline.
- A maximum of eight measurable lesions will be selected
- If no measurable lesions are present, non-measurable lesions may be chosen as index lesions.
- Selected on the basis of their size (based on longest diameters), suitability for accurate repeated measurements by imaging techniques and how representative they are for the subject's tumor burden.
- Size measured by the cross product of the longest diameter and the greatest perpendicular diameter. The sum of the products (SOP) of all index lesions will be calculated and reported for each time point.

Non-Index Lesions:

- All other soft tissues should be identified and documented.
- Presence, absence, or unequivocal progression of any non-index lesion should be noted throughout follow-up.
- Non-index measurable lesions may be measured at the discretion of the reader to aid to documentation of unequivocal progression, but will not be used in the calculation of the SOP of index lesions.

Bone Lesions:

- All lesions must be assessed at baseline and at each follow-up visit.

Clinical Endpoints Definition:

Overall Survival: Time from randomization until death due to any cause.

Response:

- Will be determined by evaluation of measurable disease, non-measurable disease, and by clinical assessment.
- Subjects with measurable disease will be assessed using standard response criteria and clinical assessment.
- Subjects with disease that is non-measurable (including bone disease) will be assessed for response based on change in CT, bone scan, and clinical assessment.
- The first tumor measurements that demonstrate a complete response or partial response will be confirmed by repeat measurement ≥ 4 weeks later.

Complete Response:

- Disappearance of all index, non-index, and bone lesions confirmed by a repeat consecutive assessment no less than four weeks after the criteria for CR are met. No new lesions. No disease-related symptoms. A subject who otherwise has a CR, but has the presence of bone lesions, will be classified as a PR.

Partial Response

- $\geq 50\%$ decrease in the SOP of index lesions compared to the baseline SOP by a repeat assessment (not necessarily consecutive) no less than four weeks after the criteria for PR are first met. No evidence of progression. No clinical deterioration. PR is not applicable to non-index lesions or bone lesions.

Stable Disease:

- Index Lesions: neither sufficient decrease in index lesions to qualify for PR nor sufficient increase in index lesions to qualify for objective disease progression.
- Non-index lesions and bone lesions: no significant change in non-index or bone lesions to qualify for either CR or objective disease progression.
- Follow-up measurements must have met the stable disease criteria at least once no less than five weeks after the first investigational product infusion.

Objective Disease Progression:

- Must be confirmed by central imaging review facility, as outlined in the Independent Radiology Review Committee (IRRC) Charter.
- Definition of objective disease progression for:
 - Index lesions: $\geq 50\%$ increase in the SOP of the index lesions over the smallest SOP observed during the study period, or the development of any new lesions on CT.
 - Non-Index lesions: Appearance of ≥ 1 lesion and/or unequivocal progression of existing non-index lesions. Worsening or new effusions or ascites will not be considered radiologic progression.

- Bone Disease: Appearance of ≥ 2 new areas of abnormal uptake on bone scan. Increased uptake of pre-existing lesions on bone scan does not constitute progression.
- Appearance of a new pathological fracture or new spinal cord compression constitutes progression.
- If a determination of objective disease progression is made by the investigator based on imaging studies, then the bone scans and abdomen and pelvis CT's will be reviewed and confirmed by the IRRC.
- PSA will not be used to assess objective disease progression.
- Determination of objective disease progression is to be made by the WHO criteria.²

Clinically Significant Disease Specific Events:

- Spinal cord or nerve root compression, if not confirmed by serial imaging studies. Pathologic fracture, if not confirmed by serial imaging studies.
- Metastatic disease in an anatomy for which no baseline scan is available for comparison to allow documentation of interval change on serial imaging studies.
- Progressive disease (as defined in 0) in an anatomy for which there is a baseline imaging assessment but serial imaging has not been performed (e.g., mediastinal or lung metastases).
- A clinical indication for radiation therapy.
- At least 2 of the following clinical signs/symptoms in comparison to baseline:
 - An increase in ECOG performance status of ≥ 1 grade.
 - Progressive anemia, defined as either
 - a decrease in hemoglobin of ≤ 2 g/dL and to a level below the lower limit of normal in the central lab reference range, or
 - a requirement for therapy with a hematopoietic growth factor (e.g., Procrit®) or transfusion with packed red blood cells for anemia.
 - $\geq 10\%$ weight loss, not attributable to intentional weight loss.
 - New urinary outflow obstruction attributable to cancer. Urinary retention may be due to disease progression, treatment-induced prostatitis, or stricture from scar tissue after surgery, so subjects should be carefully evaluated.

Clinically significant disease-specific events must be evaluated until the subject has demonstrated independently confirmed objective disease progression.

Clinical Progression: Is the first occurrence of either of the following:

- Objective disease progression (as described in 0)

² WHO handbook for reporting results of cancer treatment. Geneva; 1979.

- Development of clinically significant disease-related events. For subjects who experience two or more such clinically significant disease-related events, the date of the first disease-related event is the date of first clinically significant disease-specific event.

Immune Response: will be both cellular and humoral, specific to PA2024, prostate tissue, and tumor associated antigen.

Humoral Response: Serum antibody titers will be determined using enzyme-linked immunoabsorbent assay (ELISA).

Cellular Response:

Proliferation Assays: Peripheral blood lymphocytes will be incubated with increasing concentrations of antigen (PA2024), pulsed with ³H thymidine, and the -b(4)----- incorporated into proliferating cells determined.
Enzyme linked immunospot (ELISPOT) assay: frequency of antigen-specific, cytokine-producing cells with primary focus on interferon gamma-producing cells, using whole --b(4)----- cells as responding cells.
Exploratory analysis: may include ---b(4)-----

Long term follow-up:

- Long term follow-up includes monitoring of CBC's, all cerebrovascular events, treatment-related AE's, and survival. Long term follow-up begins for all subjects, irrespective of the treatment arm, after the subject meets objective disease progression endpoint and exits from the active assessment portion of the trial, and will continue until death.
- Subjects who decline to undergo additional protocol assessments or who have compelling reasons to discontinue study visits and/or laboratory evaluations prior to objective disease progression must continue to be followed for long-term survival.
- Information regarding administration of first chemotherapy and first anti-cancer intervention after independently confirmed objective disease progression will be collected.
- Upon entering long term follow-up, visits will occur months 2 and 6 after meeting objective disease progression and every three months thereafter.
- CBC's will be obtained at the 2- and 6-month visits after objective disease progression and every six months thereafter.
- Documentation of death in the source documentation must include date and cause. Death certificate should be obtained; if not obtained, verification by social security death index and/or date and cause of death as recorded in a hospital discharge summary should be documented.

- Subjects who withdraw consent completely for study follow-up, including survival status, will have documentation of reasons for withdrawal.

Safety Monitoring

- Evaluation with a history and physical exam will be done 7 days prior to the Week 2 and Week 4 leukaphereses.
- Beginning at Week 6, subjects will be monitored every four weeks (clinic visit or telephone calls) for the occurrence and severity of adverse events (AE's) until the objective disease progression endpoint is independently confirmed.
- At 2 and 6 months after objective disease progression is confirmed and every 3 months thereafter, subjects will be monitored for survival and evaluated for AEs that are related to the investigational product.
- Cerebrovascular events occurring throughout the study will be reported on applicant's Serious Adverse Event (SAE) form and D9902B AE Case Report Forms (CRF).

For additional details please refer to Table 1.

Analytical Plan: Study D9902B is designed to be a stand-alone study and will be analyzed separately from Study D9902A.

Randomization:

- To the sipuleucel-T or the placebo arm is to be done using Pocock and Simon's minimization method to minimize the degree of imbalance between the two treatment groups with regard to stratification factors of:
 - Primary Gleason Grade (≤ 3 , >4)
 - The number of bone metastases (0-5, 6-10, >10)
 - Bisphosphonate use (yes, no)
- Study center clusters will be formed as part of the allocation process, and centers will be assigned to clusters depending on projected enrollment and chronological order of when the first subject is pre-registered.
- The sample size for each cluster will be between 165 and 174.
- Subject allocation in a 2:1 randomization will be within a cluster.

Efficacy Analysis:

Primary Efficacy Variable: is Overall Survival (OS) as described in 0
Censoring for OS analysis for:

- Subjects alive at the time of analysis will be censored at their last documented study evaluation date or contact date, whichever is later.
- Subjects prematurely discontinued from study (lost to follow-up or have withdrawn consent) and without verification of survival status at the time of analysis will be at their last documented study evaluation date or contact date, whichever is later.

Overall survival calculations for:

- Subjects who died: [Death date – Randomization date] + 1

- Subjects who are censored: [Last study visit date or last contact date – Randomization date] +1

Primary Efficacy Analysis:

- Significance level for final analysis using a 2-sided p-value is allocated to the final analysis based on the O'Brien-Fleming alpha spending function.³
- Statistical significance is achieved if the difference in OS between the two treatment groups is less than the pre-specified significance level.
- Primary test for OS data will use the Wald's test based on the stratified Cox regression model adjusted for two covariates, PSA and LDH.
 - Stratification variables will include:
 - Primary Gleason Grade (≤ 3 , ≥ 4)
 - The number of bone metastases (0-5, 6-10, >10)
 - Bisphosphonate use (yes, no)

Imputation for missing covariates: will be based on the median of the data collected from subjects without any missing values.

Hazard ratio estimation of treatment effect: will be generated using the same Cox regression model adjusted for two covariates. The placebo arm will be used as the denominator. Two-sided 95% confidence intervals (CI) will be calculated using the above-referenced Cox regression model.

Estimation of OS distribution: will use the Kaplan-Meier (KM) method. KM methods will be used to display survival curves and estimate median time to endpoints that are based on time to event analysis, including median OS.

Supportive analysis:

- Will be conducted based on only those subjects without any missing baseline covariates
- p-value associated with the log-rank, stratified by the above-mentioned stratification variables will be determined
- Hazard ratio, with its 95% CI derived from stratified unadjusted Cox regression model will be provided.

Additional Analyses: will be conducted if there are more than 304 death events in the final database.

Interim Analysis (IA):

- One IA is planned at approximately 228 death events (75% of the total number of planned death events) have been observed.
- Significance level for interim analysis using a 2-sided p-value is allocated to the analysis based on the O'Brien-Fleming alpha spending function.

³ O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979;35(3):549-56.

- Statistical significance is achieved if the difference in OS between the two treatment groups is less than the pre-specified significance level.

Secondary Efficacy Variable: Time to Objective Disease Progression

Time to Objective Disease Progression: is defined as time from randomization to achieving objective disease progression, as determined by the IRRC. Death events will be considered a competing event.

Censoring for Time to Objective Disease Progression for:

- Subjects who do not experience objective disease progression at the time of analysis will be based on the time of the last imaging study obtained per protocol. Non-protocol-specified imaging studies (MRI, Ultrasound, Xrays) will not be included in the analysis.
- Subjects who do not experience objective disease progression at the time they have been lost to follow-up, withdrew consent, or discontinued follow-up will be based on the date of the last imaging study.
- Subjects whose date of objective progression cannot be determined by the IRRC, the subject will be considered without objective disease progression and censored at the date of the last imaging study.

Time to Objective Disease Progression Calculations (TTP):

- TTP for subjects with objective disease progression = [IRRC date of objective disease progression – Randomization date]+1
- TTP for subjects who are censored = [last imaging study date – randomization date] + 1

Secondary Efficacy Analysis:

- Will use a log rank test stratified by the stratification variables as described in 0
- 2-sided p-value associated with the treatment effect using the above mentioned log rank test will be used to assess the treatment effect.
- Assessment of HR and its 95% CI will use the stratified Cox regression model unadjusted for the covariates.
- TTP distribution will be based on the cumulative incidence method.

Tertiary Efficacy Variables: are time to clinical progression, PSA doubling time, and immune response.

Time to Clinical Progression (TTCP): time from randomization to clinical progression, as defined in Section **Error! Reference source not found.** Death is considered a competing event.

Censoring for TTCP Analysis:

- For subjects who do not experience clinical disease progression, censoring will be done at the time of last clinical assessment (clinical study visit or imaging study, whichever occurs later).

TTCP calculations:

- For subjects who experience clinical progression, TTCP = [Clinical progression date – Randomization date] + 1
- For subjects who are censored, TTCP= [last clinical assessment date – Randomization date] + 1

TTCP analysis: same statistical methods used for analysis of TTP will be used.

PSA doubling time (PSADT) and calculation of PSADT:

- Population PSA time slope: for each treatment arm will be computed based on a mixed effects model with all PSA measurements from baseline until the institution of other systemic anti-cancer therapy.
- Fixed effects will include stratification factors, time as a continuous variable, treatment, and treatment by time interaction.
- Estimated PSADT and its 2-sided 95% CI for each treatment arm will be computed using the estimated population PSA time slope for the response variable of log transformed PSA.
 - The following formula will be used in the calculation of PSADT:
$$\text{PSA DT} = \log / (\text{Population slope of the regression line for log PSA vs time})$$
 - A mixed effects model that can estimate both pre- and post-randomization PSA (log) slopes will be examined.

Immune response:

T cell stimulation index for proliferation assays:

- (b) (4)----- will be determined for both the treatment and the placebo arm.
- (b) (4)----- model approach for log-transformed stimulation index will be evaluated to detect if sipuleucel-T-induced, antigen-specific, cellular immune response is greater than that induced by the placebo. The (b) (4)----- approach will include treatment effect, visit, treatment by visit interaction, and subject as random effects.
- Immune responses at each post-baseline visit will be compared between treatment groups or to baseline using a contrast statement.
- Calculation for ratio of stimulation index for the proliferation assays will be calculated for each subject as follows:
(b) (4)-----
(b) (4)-----
- The Wilcoxon rank sum test will be used to compare the two treatment groups at each scheduled visit.

ELISPOT Assays:

The frequency of antigen-specific cytokine-producing cells will be determined using enzyme-linked immunospot assay (ELISPOT), with the primary analysis focusing on interferon gamma-producing cells using (b) (4)----- cells as responding cells

PROTOCOL AMENDMENTS

List of Protocol Amendment

Amendment 5 dated 05/21/03. The changes made are as follows:

Changes to Endpoints:

- New secondary endpoints of survival time and time to opioid analgesic use added.
- Time to treatment-related failure deleted as a secondary endpoint.
- Disease-related pain moved from secondary endpoint to co-primary endpoint.
- New tertiary endpoints of comparison of tumor response rate, duration of response, skeletal morbidity rate, proportion of subjects requiring opioid analgesics, and time to analgesic shift, between the two treatment groups were added.
- Time to development of clinical progression (tertiary endpoint) criteria revised to include specific criteria to define the condition.
- PSA criterion removed as criterion for response criterion.

Changes to eligibility:

- Eliminate the requirement for \geq positive staining for PAP in tumor cells, since 100% of Gleason ≤ 7 neoplasms express PAP of $\geq 25\%$ of tumor cells.
- Require Gleason sum score of ≤ 7 confirmed by central lab prior to randomization.
- Specify the definition of androgen independent prostate cancer and definition of metastatic disease; clarify definition of measurable disease and evaluable disease.
- Clarify that subjects receiving medical castration therapy must continue such therapy throughout the blinded study.
- Duration of prior or concurrent therapy with bisphosphonates reduced from 30 to 28 days prior to registration.
- Mandatory continuation of bisphosphonate therapy without alterations in dosing during the blinded portion of the trial
- Entry criterion for hepatic enzymes changed from 5 x Upper Limit of Normal (ULN) to 2.5 x ULN
- Change from excluding “visceral metastases” to metastasis to the liver, lung, or brain.
- Definition of symptomatic metastatic disease revised.
- Specify duration of stopping anti-androgen therapy based on type of non-steroidal anti-androgen and specify definition of anti-androgen withdrawal syndrome.
- Remove 3-month chemotherapy washout for subjects with an adequate CD4+ T-cell count. Prior chemotherapy allowed only if at least six months have elapsed from treatment to registration.
- Exclusion of subjects who receive > 2 chemotherapy regimens at any time prior to participation in this trial.
- Clarified that subjects who received any prior systemic corticosteroid therapy or 5- α reductase inhibitors, or high dose calcitriol or ketoconazole within 28 days of registration, or have a pathological long bone fracture or Pagets disease of the bone, were to be excluded.
- Clarification regarding infection or fever at baseline and prior cancer history.
- Clarity added to tentative leukapheresis scheduling, completion of baseline procedures.

BLA 125197, Sipuleucel-T
CBER Clinical Review

- Reduce allowable time windows for CT scans from 42 days to 14 days and for ECG from 42 days to 28 days or less, prior to date of registration.
- Only CT scans to be used to evaluate the abdomen and pelvis and to exclude pulmonary metastases.

Changes to Monitoring Schedule:

- Modify the schedule when subjects will be monitored for the first development of disease progression and/or disease-related pain, based on the agreement with the agency regarding earlier and more frequent assessments for the co-primary endpoint.

Changes to Response evaluation:

- Definition of Progression was changed from being inclusive of clinical events to strictly related to progression confirmed by serial imaging.
- Un-blinding of subjects receiving APC-Placebo should have met both co-primary endpoints to qualify for entry (objective disease progression) into salvage protocol.
- Criteria for measurable and non-measurable disease revised; criteria for bone lesion included; removed criterion for disease-related pain as a progression endpoint; included prostate cancer-related events (e.g., pathological fracture) in the absence of confirmed radiologic evidence as criteria for disease progression (confirmed radiological progression is needed for primary analysis of disease progression)

Changes to Treatment plan:

- Infusion time increased from 30 minutes to 60 minutes to reduce the incidence of infusion-related events.

Changes to Statistical Considerations:

- Two co-primary endpoints included, and revisions to secondary and tertiary endpoints included.

Other changes:

- Reporting of adverse events

Amendment 6 dated 04/29/04. The changes made are as follows:

Changes to Endpoints:

- Tertiary endpoints removed

Changes to Eligibility:

- Revised inclusion criterion for subjects with prior chemotherapy within 3 months of registration based on meeting requirements for CD4+ T cell count, post-chemotherapy PSA nadir, post-chemotherapy bone scan, and post-chemotherapy nodal criterion based on CT imaging.

Changes to Monitoring Schedule:

- Clarified that subjects meeting co-primary endpoints will enter long-term follow-up
- Unblinding procedures clarified

Changes to Statistical Considerations:

- Possibility of interim analysis to review safety and efficacy information by DMC

Changes to reporting of adverse events: minor changes.

Amendment 7 dated 10/11/05. The changes made are as follows:

Changes to Endpoints:

BLA 125197, Sipuleucel-T
CBER Clinical Review

- Primary endpoint revised to Overall Survival (OS)
- Secondary endpoint revised to Time to Progression (TTP) and Time to Disease Related Pain and Time to First Use of Opioid Analgesics removed as secondary endpoints.
- Tertiary endpoints of tumor response rate, duration of response, and skeletal morbidity rate removed, and added PSA doubling time and immune response to PA2024, with specific criteria to define both revised tertiary endpoints.

Changes to Eligibility:

- Revised inclusion criteria to include subjects with Gleason sum score of >7 and minimally symptomatic disease defined by specific criteria; define period of castration as at least three months prior to registration
- Revised exclusion criteria to exclude subjects with malignant pleural effusions and malignant ascites, moderate-severe disease-related pain, and subjects with specific criteria to define ongoing anti-androgen withdrawal response.

Changes to Treatment plan:

- Adjustment of infusion times for subjects who experience an infusion-related adverse event
- Clarified that subjects who receive systemic therapy for prostate cancer prior to meeting objective disease criterion should remain on-study and remain blinded until objective disease criterion is met.

Changes to Statistical Considerations:

- Interim Analysis for primary and secondary endpoints added to occur when 180 death events have occurred.
- Cox proportional hazards model added for analysis of primary and secondary endpoints

Changes to reporting of adverse events: minor changes.

Amendment 8 dated 01/03/08. The changes made are as follows:

Changes to Endpoints:

- Clinically Significant Disease Specific Event criterion modified to remove requirement for pathologically confirmed urinary outflow obstruction

Changes to Monitoring plan:

- Long term follow-up schedule defined as three months for treatment-related adverse events and survival status.

Changes to Statistical Considerations:

- Target enrollment changed from 455-550 subjects to approximately 500 subjects
- Final analysis time point changed from 360 to 304 events, with change in power from 90% to 88%.
- Number of covariates for the Cox proportional hazards model for primary analysis to included only two covariates (LDH(ln) and PSA(ln))
- Addition of CD54+ upregulation and analysis of the impact of docetaxel chemotherapy to additional survival analyses
- Analyses of Cerebrovascular events added.

Changes to reporting of adverse events:

- Reporting of Cerebrovascular events occurring throughout D9902B study to be reported in the SAE form and D9902B AE CRF, while those occurring during the PB01 study to be reported in the PB01 AE CRF rather than D9902B AE CRF.

D: Review of Major Protocol Deviations

Placebo Arm:

- 92074-0311: This patient had symptomatic metastatic disease based on the baseline pain log, with an average pain score of two within the previous seven days, making the subject eligible for the study. However, the exclusion criteria checklist stated that the subject did not have symptomatic metastatic disease.

The subject was administered external beam radiation (prohibited therapy while on study) on 07/22/04 and independently confirmed to have pain progression; however, the independent confirmation of radiological progression did not occur until 08/12/04.

Reviewer's comment: The subject would still meet eligibility criteria since the subject had minimally symptomatic disease. The subject received radiation therapy less than 1 month prior to confirmation of radiologic progression by the independent review team. However, palliative radiation therapy has not been established to affect long term survival; therefore, this deviation would be unlikely to affect results of the primary efficacy analysis.

- 92102-0535: Subject's pain log at entry that did not indicate pain. However, subsequent to study entry, the subject was found to have symptomatic metastatic disease that would have excluded the subject from trial entry based on Amendment 6, which required that subjects have no pain symptoms related to prostate cancer. Disease-related pain was independently confirmed on 09/05/05; clinically significant disease specific event was noted on 08/17/06 requiring external beam radiation (EBRT). Docetaxel was administered on 08/30/07, prior to independent confirmation of disease progression (Date of last imaging: 08/16/06), and is a major protocol deviation.

Reviewer's comment: Although the subject had symptomatic metastatic disease that would have disqualified the subject from trial entry based on the exclusion criteria in Amendment 6, this criterion was later revised to include minimally symptomatic subjects with average pain scores of 4. In this subject's case, there is no documentation of the level of pain at trial entry to assess whether the subject had minimally symptomatic disease (which would have allowed inclusion of the subject in the study based on the revised criteria under Amendment 7), or more than minimally symptomatic disease (which would have excluded the subject from the study based on revised criteria under Amendment 7). It is unclear whether this subject would have been eligible under the final study protocol

92136-1228: The subject did not receive medical castration therapy for a period of at least 3 months prior to trial entry. On the date of randomization was 08/10/07, the subject was on complete androgen blockade therapy, based on the prostate cancer history. Hormonal therapy was stopped on 09/26/06, and PSA on 10/30/06 showed elevation to 23.51. However, the three PSA readings prior to trial entry were 3.34 (05/13/07), 6.66 (06/20/07), and 9.14 (07/11/07), establishing that the subject had rising PSA. Total testosterone level was 39 on 07/17/07.

Reviewer's comments: A major protocol deviation is noted in this subject in that medical castration therapy was not ongoing at the time of trial entry. However, from a clinical standpoint, the subject was adequately castrated based on the testosterone levels.

92153-0746: The subject had moderate or severe pain on the revised checklist for exclusion criteria. Pain log indicates the worst pain to be 5, and the average pain to be 5 within the 7 days.

Reviewer's comments: This is a major eligibility deviation.

Sipuleucel-T Arm:

92026-0641: Subject was noted to have symptomatic metastatic disease after study entry. Pain log at registration indicates average pain of 1 for the previous 7 days. The verification checklist for the exclusion criteria was revised to note that the subject had symptomatic metastatic disease. The subject received a prohibited therapy (EBRT) on 08/09/06. Although the imaging was done on 08/08/06, prior to initiation of EBRT, the actual independent confirmation of progression was done after the initiation of EBRT. The protocol specified that independent confirmation of disease progression is to be made prior to instituting any therapy other than study therapy for the treatment of prostate cancer.

Reviewer's comment: The subject was eligible for the study, since the subject meets the minimally symptomatic disease criteria based on the pain log. EBRT was administered before the actual date of independent confirmation of progression, but did not occur before the actual date of the scan confirming progression.

92025-0686: The subject did not have adequate baseline liver function to meet eligibility criteria. The AST was 92 U/L, with the allowable upper limit for study entry being 90 U/L (2.5 x ULN), based on the upper limit of the laboratory being 36U/L. Follow-up AST done on Week 6 showed a level of 48U/L.

Reviewer's comment: This is a major eligibility deviation. However, the AST limit was only slightly higher than the allowable limit, and the deviation does not have a major impact on the primary efficacy endpoint.

92048-0246: The subject had symptomatic metastatic disease with an average pain of 1 for the 7 days prior to registration, based on the pain log at registration. The exclusion criteria checklist stated that the subject did not have symptomatic metastatic disease.

Reviewer's comment: The incident is a major eligibility deviation, based on the inclusion criterion in protocol Amendment 5. This criterion was later revised to allow minimally symptomatic subjects to enter the study. Therefore, the subject would have met final protocol entry criteria.

92024-0376: Subject had a lung lesion and eligibility criterion excludes subjects with lung metastases.

Reviewer's comments: This is a major eligibility deviation.

92056-0866: Subject had history of basal cell carcinoma per the applicant's listing of protocol deviations (D9902B CSR, 16.2.2 Listings, Page 40 of 178). CRF review of baseline history did not document basal cell carcinoma under disease history.

BLA 125197, Sipuleucel-T
CBER Clinical Review

Reviewer's comments: Protocol eligibility criteria stated that basal or squamous cell skin cancers must have been adequately treated and the subject must be disease-free at the time of registration. Subjects with a history of stage I or II cancer must have been adequately treated and been disease-free for ≥ 3 years at the time of registration. *Since there is no additional data regarding the status of the basal cell carcinoma, this subject should be considered as a minor deviation.*

92108-0549: The androgen independent state at baseline could not be verified, since the CRF for Androgen independence-PSA was deleted. The CRF containing the Prostate Cancer History indicates that the subject had received Complete Androgen Blockade and second line hormonal therapies.

Reviewer's comments: This is a major eligibility deviation. On 04/12/05, less than four weeks prior to randomization, the PSA level was 272.9 ng/mL and testosterone level was <8 ng/dL, which is suggestive of androgen independence and PSA progression. PSA at Week 6 after randomization indicated an elevated PSA of 348 ng/mL, evaluated by the same laboratory. Based on these findings, of highly elevated PSA levels at baseline with serum testosterone levels <50 ng/mL and ongoing androgen therapy, from a clinical standpoint the subject had an androgen independent state.

Review of Serum Testosterone levels at Baseline:

All 512 subjects in the study have verification of laboratory data by the reviewer. Discrepancies were noted for the following subjects:

Placebo Arm:

92048-0364: Testosterone level of <8 ng/mL was noted on 07/08/04; however, the subject was not randomized until 08/10/04.

Reviewer's comments: The testosterone levels were acceptable, but completed 2 days before the allowable period for enrollment.

Sipuleucel-T Arm:

92027-0470: Testosterone level of 297 ng/mL was noted on 04/12/05 in the laboratory report, with a handwritten testosterone level of 0.2 ng/mL on 4/6/05 based on "SCCA" level. However, the submitted sheet for baseline labs from the treatment site does not have an entry for testosterone levels. PSA level on entry, as documented in the CRF, was 21.59 ng/mL on 12/07/04, and the subject was on anti-androgen therapy at that time. The CRF containing the check boxes for inclusion criteria confirms that the subject had testosterone levels of less than 50 ng/mL. The subject was randomized on 01/03/05, prior to obtaining the baseline testosterone levels.

Reviewer's comments: No baseline testosterone levels were obtained, and the testosterone levels obtained subsequently had values that were above the entry criterion. Although there appears to have been PSA progression on anti-androgen therapy, it is unclear whether the subject was adequately castrated.

92048-0244: Testosterone level of 16 ng/mL was noted on 05/14/04; however, the subject was randomized on 02/09/04. The subject had rising PSA on anti-androgen therapy, based on the CRF report. Reviews of the data clarification forms do not indicate any attempts to clarify the testosterone levels.

Reviewer’s comments: The testosterone levels were within eligibility criteria approximately three months after study enrollment, while on anti-androgen therapy.

Review of Death Data

Table 41: FDA review of individual death data

<i>Subject ID</i>	<i>Treatment</i>	<i>Date of death in Primary Efficacy Analysis Data set</i>	<i>Date of death in the documents provided for verification</i>
92146-0413	Placebo	-b(6)---	-b(6)--
92109-0220	Sipuleucel-T	-b(6)---	-b(6)--

The discrepancy in the date of death in the case of the subject in the placebo arm is only one day and is not expected to make a significant difference in the outcome of the primary efficacy analysis. In the case of the subject in the sipuleucel-T arm, the difference in survival of about one month may alter the primary efficacy outcome in favor of the sipuleucel-T arm. However, in both cases, the CRF remains the primary source of documentation for date of death for the primary efficacy analysis.

- 10 subjects who had date of randomization and date of death did not have survival durations recorded.

The applicant clarified that in this data set (“DEATH data set”), the DTHDYS variable was derived for use in summaries of safety and took into account the day of first infusion of the double-blind study treatments. The 10 subjects identified above did not receive infusions and therefore did not have DTHDYS calculated. However, the analysis of overall survival was based on the KEYVAR2B data set, in which the SURVDUR variable had survival days calculated from date of randomization, and all 10 subjects had survival durations computed for this variable and included in the analysis.

- 10 subjects had a discrepancy between the dates of randomization in the data set and the investigator’s date of randomization based on the CRF.

The applicant clarified that date of randomization recorded on the CRF was reconciled with randomization dates provided by the tracking system (-b(4)-). The DCF query numbers for these clarifications that led to the reconciliation were provided and verified by the clinical reviewer.

- 3 subjects did not have exact date of death (incomplete date of death) documented in the CRF, but had date of death in the data set. The applicant was asked to clarify whether the death date was imputed in the data sets.

The applicant clarified that the final determination of the date of death was completed through the query process. This process provided complete dates of deaths, and no imputation of the date of deaths was needed. Of the three subjects, one subject had verification of the date of death by SSDI; one subject had verification by obituary as stated in the DCF query; and one subject had verification from the study coordinator based on the DCF query.

- 7 subjects who had deaths confirmed in the data sets by SSDI did not have SSDI reports included in the CRF. The applicant was asked to provide copies of the SSDI for these subjects.

The applicant submitted SSDI for all 7 subjects.

- 4 subjects who had deaths confirmed in the data sets by death certificates did not have copies of the death certificates available in the CRF. The applicant was asked to provide copies of the death certificate, SSDI, or hospital records, or provide justification for the lack of documentation.

The applicant submitted death certificates for 2 subjects, SSDI for 1 subject and an obituary report and hospital record for 1 subject.

- 1 subject who had death confirmed in the data set by obituary did not have copies of the obituary in the CRF. The applicant was asked to clarify why a copy of the obituary or death certificate or SSDI could not be provided.

The applicant submitted an obituary report and SSDI.

- 4 subjects had deaths confirmed in the data sets by obituary but did not have the protocol-specified confirmatory documentation. The applicant was asked to provide clarification as to whether the SSDI database was queried.

The applicant submitted SSDI for the four subjects.

- 13 subjects had deaths documented by the Principal Investigator (PI) in the CRF but no confirmatory documentation. The applicant was asked to provide an explanation as to why no confirmatory documentation could be provided.

The applicant submitted the death certificate or SSDI for 12 subjects and an obituary report for one subject.

E. Narratives of Death Associated with CVE's

- Subject D9902B.0036.0624 (placebo group), age 68, with a history of hypertension and prostate cancer, underwent leukapheresis on Oct. 18, 2005, and received the first study product infusion on Oct. 21, 2005. He presented to the emergency room on Oct. 28, 2005 with weakness and decreased sensation in the left arm, and was hospitalized for further work-up. On the following day, the subject's symptoms worsened, and he was treated with TPA. Subsequent head CT

BLA 125197, Sipuleucel-T
CBER Clinical Review

indicated worsening hemorrhage. Subject's course continued to worsen. Approximately one month later, the subject was transferred to hospice care. He died a -b(6)- later, on --b(6)-----

- Subject D9901.69.073 (placebo group), age 66, received the third infusion on April 5, 2001. He developed TIA seven months after receiving his last infusion on January 7, 2002 and was initially treated with Aspirin. On --b(6)-----, he developed intracranial bleeding and died.
- Subject D9902B.0125.0236 (sipuleucel-T group), age 59, received three product infusions, with last infusion on 2/26/2004. The subject died on -b(6)----- due to CVA. No detailed information or death summary is available. Death information was confirmed by subject's wife per CRF. Subject had left salivary gland carcinoma stage II, in addition to prostate cancer.
- Subject D9902B.0057.0712 (sipuleucel-T group), age 79, with a history of hypercholesterolemia, received three study infusions, with last infusion on 03/22/2006. He had mild transient chest pain on Feb. 26, 2006, followed by transient slurred speech on March 22, 2006. He had a stroke on April 6. He was admitted for hospice care on April 12, 2006 and died in the hospital on --b(6)------. The subject remained essentially unconscious throughout the period of hospice care.
- Subject D9901.0060.0039 (sipuleucel-T group), age 79, had a history of atrial fibrillation. He died on --b(6)-----, of stroke, possibly of subarachnoid hemorrhage (event not well documented).
- Subject D9902B.0064.0965 (sipuleucel-T group), age 73, with a history of hypertension, received his third study product infusion on 11/15/2006. He did not have disease progression. A right parietal wall meningioma was documented on 08/04/2007. Subject had an intracranial bleed on 11/28/2007. He was hospitalized with left occipital mass with hemorrhagic conversion, and seizure. Subject subsequently developed respiratory failure requiring intubation. He died on --b(6)-----
- Subject D9901.0024.0001 (sipuleucel-T group), age 77, had disease progression. He died on -b(6)------. Cause of death was listed as acute cerebrovascular accident. No other information regarding the death or cause of death was available.
- Subject D9901.0027.0028 (sipuleucel-T group), age 70, received the third infusion on Sept. 8, 2000 and died -b(6)-----, about 9 months after receiving his last infusion. He had an ischemic stroke, was treated with TPA, and then developed a massive stroke and died.
- Subject D9901.0060.0039 (sipuleucel-T group), age 79, received the third infusion on Nov. 15, 2000 and died of "stroke" per obituary in --b(6)-----.
- Subject D9901.0024.0001 (sipuleucel-T group), age 77, received the third infusion on Feb. 5, 2000 and died of acute cerebral accident on -b(6)-----, about 10 months after receiving his last study product infusion.

F. Narratives of Cases Associated with Acute Cardiac Arrhythmias

- Subject 92109-0220 had a history of atrial fibrillation since 1993. He received his third and final infusion of sipuleucel-T on 08 Jan 2004. He experienced chills on 08 Jan 2004 and 09 Jan 2004 but did not report any other acute infusion reaction events. He was hospitalized for atrial fibrillation with rapid ventricular response on 09 Jan 2004. He did not respond to diltiazem but did convert to normal sinus rhythm following cardioversion on 10 Jan 2004. The Investigator did not consider this event to be related to study product.
- Subject 9160-039 had a history of atrial fibrillation. He received his second infusion of sipuleucel-T on 01 Nov 2000. He experienced chills and wheezing on the day of this infusion. He developed atrial fibrillation on 02 NOV 2000. He was treated with digoxin, furosemide, and oxygen. This event was considered to be alcohol-induced, and the Investigator considered this event as unlikely to be related to study product. The subject went on to receive his third infusion of sipuleucel-T.
- Subject 92038-1034 had a past history of hypertension for which he was taking atenolol at the time of study registration. He developed ventricular tachycardia on the day of his first infusion of sipuleucel-T. The ventricular tachycardia lasted 1 minute and was considered not serious. The timing of this event relative to the infusion is not known. He experienced a syncopal episode the same day, for which he received IV fluids; potassium was administered to treat hypokalemia. No medication was administered for the ventricular tachycardia. He did not experience any acute infusion reaction events that day. He went on to receive his second and third infusions, with chills reported during both infusions, but he did not report any further arrhythmias.

G. Literature Review/References

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- 1 Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin.* 2009; 59:225-249
 - 2 Ward JF, Moul JW, Rising prostate-specific antigen after primary prostate cancer therapy; *Nature Clinical Practice Urology*, 2005; 2(4):174-82.
 - 3 Kelly WK, Scher HI, Mazumdar M, Vlamis V, Schwartz M, Fossa SD, Prostate-Specific Antigen as a Measure of Disease Outcome in Metastatic Hormone-Refractory Prostate Cancer, *J Clin Oncol.* 1993 Apr, 11(4): 607-15
 - 4 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.
 - 5 Small EJ, Srinivas S, The anti-androgen Withdrawal Syndrome, *Cancer*, 1995; 76(8):1428-1434.
 - 6 Smaltz O, Scher H, Small EJ, Verbel DV, McMillan A., Regan K, Kelly KW and Kattan M, Normogram for Overall Survival of Patients with Progressive Metastatic Prostate Cancer After Castration. *J Clin Oncol*, 2002;20(19):3972-82.
 - 7 NCCN Practice Guidelines in Oncology-v.1.2010
 - 8 Dagher R, Li N, Abraham S, Rahman A, Sridhara R, Pazdur R. Approval summary: Docetaxel in combination with prednisone for the treatment of androgen-independent hormone-refractory prostate cancer. *Clin Cancer Res.* 2004;10(24):8147-51.
 - 9 WHO handbook for reporting results of cancer treatment. Geneva; 1979.
 - 10 Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 1975; 31(1):103- 15.
 - 11 O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979;35(3):549-56.
 - 12 Stark JR; Perner S; Stampfer MJ; Sinnott JA; Finn S; Eisenstein AS; Ma J; Fiorentino M; Kurth T; Loda M; Giovannucci EL; Rubin MA; Mucci LA, Gleason score and lethal prostate cancer: does $3 + 4 = 4 + 3$?, *J Clin Oncol.* 2009;27(21):3459-64. Epub 2009 May 11.
 - 13 Soloway MS, Haredeman SW, Hicker D, Raymond J, Todd B, Soloway S, Moinuddin M., Stratification of patients with metastatic prostate cancer based on extent of disease on initial bone scan, *Cancer.*1988;61(1):195-202.
 - 14 Bader P; Burkhard FC; Markwalder R; Studer UE, Disease progression and survival of patients with positive lymph nodes after radical prostatectomy. Is there a chance of cure?. *J Urol* 2003;169(3):849-54.
 - 15 Berthold DR, Pond GR, Roessner M, de Wit R, Eisenberger M, Tannock IF, Treatment of Hormone-Refractory Prostate Cancer with Docetaxel or Mitoxantrone: Relationships between Prostate-Specific Antigen, Pain and Quality of Life +Response and Survival in the TAX-327 Study. *Clin Cancer Res* 2008;14(9):2763-7.