

# Protocol

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**A RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED PHASE 3 TRIAL OF  
IMMUNOTHERAPY WITH AUTOLOGOUS ANTIGEN PRESENTING CELLS  
LOADED WITH PA2024 (PROVENGE<sup>®</sup>, SIPULEUCEL-T, APC8015) IN MEN WITH  
METASTATIC ANDROGEN INDEPENDENT PROSTATIC ADENOCARCINOMA**

STUDY PRODUCT: APC8015 (sipuleucel-T; antigen presenting cells loaded with prostate antigen PA2024)

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## LIST OF ABBREVIATIONS

<b>Abbreviation</b>	<b>Definition</b>
AE	adverse event
ALT	alanine aminotransaminase (SGPT)
ANC	absolute neutrophil count
APC	antigen presenting cell
AST	aspartate aminotransaminase (SGOT)
CBC	complete blood count
CI	Confidence interval
CR	complete response
CRF	case report form
CT	computed tomography
DES	diethyl stilbestrol
ECOG	Eastern Cooperative Oncology Group
ELISA	enzyme-linked immunosorbent assay
ELISPOT	enzyme-linked immunospot
GM-CSF	granulocyte-macrophage colony-stimulating factor
HgB	hemoglobin
HIV	human immunodeficiency virus
HR	hazard ratio
HTLV	human T cell lymphotropic virus
IRB	Institutional Review Board
IRRC	Independent Radiology Review Committee
ITT	intent-to-treat
IV	intravenous
LDH	lactic dehydrogenase
ln	natural logarithm
MedDRA	Medical Dictionary for Regulatory Activities

<b>Abbreviation</b>	<b>Definition</b>
MR	magnetic resonance
NCI CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
OS	overall survival
PAP	prostatic acid phosphatase
PBMC	peripheral blood mononuclear cell
PR	partial response
PSA	prostate specific antigen
PSADT	PSA doubling time
QC	quality control
rGM-CSF	rat granulocyte-macrophage colony-stimulating factor
rPAP	rat prostatic acid phosphatase
SAE	serious adverse event
SD	stable disease
SOP	sum of the products
TTCP	time to clinical progression
TTP	time to objective disease progression
UCSF	University of California, San Francisco
ULN	upper limit of normal
VAS	visual analog scale
WBC	white blood cell

## **1.0 SYNOPSIS**

### **1.1 Study Phase**

Phase 3.

### **1.2 Investigational Product, Dosage, and Route of Administration**

Sipuleucel-T (APC8015, Provenge<sup>®</sup>) is an autologous cell product consisting of antigen presenting cells (APCs) loaded with prostate antigen PA2024, a recombinant fusion protein composed of prostatic acid phosphatase (PAP) linked to granulocyte-macrophage colony-stimulating factor (GM-CSF). GM-CSF acts as a targeting molecule that directs the PAP antigen to APCs and promotes antigen uptake and processing. A dose of sipuleucel-T is prepared from cells from a single leukapheresis procedure, with a minimum of 20 million CD54<sup>+</sup> cells (the biologically active component of sipuleucel-T), which is administered via a single intravenous infusion at Weeks 0, 2, and 4.

### **1.3 Project Code**

D9902.

### **1.4 Indication**

Treatment of asymptomatic or minimally symptomatic, metastatic, androgen independent prostatic adenocarcinoma.

### **1.5 Study Objectives**

#### **1.5.1 Primary Objective**

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

#### **1.5.2 Secondary Objective**

To assess the safety and efficacy of sipuleucel-T in delaying time to objective disease progression in men with metastatic androgen independent prostate cancer.

### **1.6 Study Population**

Men  $\geq$  18 years of age with asymptomatic or minimally symptomatic, metastatic, androgen independent prostatic adenocarcinoma.

### **1.7 Study Design**

Multicenter, randomized, double blind, placebo-controlled, parallel group.

Randomization will utilize an adaptive algorithm (minimization technique) to balance for 3 prognostic factors at baseline:

- Primary Gleason grade;
- Number of bone metastases; and
- Bisphosphonate use.

### **1.8 Concurrent Control**

Subjects randomized to receive the control infusion will be administered non-loaded APCs (APC-Placebo [placebo]) in a single intravenous infusion at Weeks 0, 2, and 4.

### **1.9 Duration of Treatment**

Subjects will receive sipuleucel-T or placebo every 2 weeks x 3.

### **1.10 Methodology**

Subjects will be evaluated for eligibility criteria and randomized in a 2:1 ratio to receive sipuleucel-T or placebo. The primary efficacy endpoint is overall survival. The secondary efficacy endpoint is time to development of objective disease progression as assessed by serial imaging studies. Safety assessments include adverse event (AE) monitoring, physical exam, complete blood count (CBC), serum biochemistries, and urinalysis. After the development of objective disease progression, the subject may be unblinded and will be monitored for treatment-related AEs and survival. During this interval, the subject may receive appropriate medical treatment for symptoms or underlying disease. Subjects who have demonstrated independently confirmed objective disease progression are unblinded, and if placebo was received may have the option of receiving treatment with APC8015F (sipuleucel-T prepared from cryopreserved quiescent APCs) as part of a salvage protocol.

Protocol D9902 is being conducted in 2 parts: Part A (D9902A) includes subjects enrolled in the original protocol through Amendment 4 (12 MAR 2001). D9902A included subjects with asymptomatic, metastatic androgen independent prostate cancer. Part B (D9902B) commenced with Amendment 5 (21 MAY 2003) and initially included subjects with Gleason Sum  $\leq 7$  malignancies only. Studies D9902A and D9902B will be analyzed separately. The study design, conduct, and analysis described in this protocol amendment refer specifically to D9902B.

Beginning with Amendment 7 (11 OCT 2005), subjects were enrolled in D9902B regardless of Gleason Sum, and minimally symptomatic subjects, in addition to asymptomatic subjects, were eligible for enrollment. Beginning with Amendment 8 (20 NOV 2007), all cerebrovascular events occurring throughout the study (regardless of causality), must be reported on Dendreon's serious adverse event (SAE) form and the D9902B AE case report form (CRF). (Cerebrovascular events occurring during a subject's participation on the Protocol PB01 study will be reported on the Protocol PB01 AE CRF rather than the D9902B AE CRF.)

### **1.11 Number of Study Centers**

Approximately 90.

### **1.12 Total Number of Subjects and Statistical Rationale**

#### **Planned total:**

Approximately 500 subjects will be enrolled (2:1 treatment vs. placebo) in order to obtain the approximately 304 deaths required for the final survival analysis.

#### **Sample size considerations:**

Overall survival: 88% power at  $\alpha = 0.05$ , assuming a hazard ratio (HR) for death of 0.69 (sipuleucel-T versus placebo). Using the Cox proportional hazards model, an interim analysis will be performed at approximately 228 death events, with  $\alpha = 0.019$ ; a final analysis will be performed at approximately 304 events, with  $\alpha = 0.044$ .

Each subject will be followed for efficacy and safety until independently confirmed objective disease progression. All subjects will be followed long term for survival.

### **1.13 Adverse Events**

All AEs will be recorded from registration until objective disease progression has been independently confirmed. Thereafter, all cerebrovascular events (regardless of causality), except those occurring during a subject's participation on the Protocol PB01 study (which will be reported on the Protocol PB01 AE CRF rather than the D9902B AE CR), and AEs that are, in the Investigator's opinion, related to the investigational product will be recorded. All cerebrovascular events should be reported as a serious adverse event (SAE) as well.

### **1.14 Plan for Data Analysis**

#### **1.14.1 Primary Efficacy Endpoint**

Overall survival (time to death).

#### **1.14.2 Secondary Efficacy Endpoint**

Time to objective disease progression.

#### **1.14.3 Tertiary Efficacy Endpoints**

Time to clinical progression.

Prostate specific antigen (PSA) doubling time (PSADT).

Immune response to PA2024.

#### 1.14.4 Safety Analyses

Adverse events.

Laboratory evaluations.

Vital signs.

## 2.0 BACKGROUND

### 2.1 Prostate Cancer

In the United States, prostate cancer is the most common solid tumor malignancy in men. It is expected to account for over 218,890 new cases and 27,050 deaths in 2007 (Jemal 2007). Approximately 70% of patients will have metastases at some time during the course of their disease (Gittes 1991). Androgen deprivation is the standard therapy for metastatic prostate cancer and achieves temporary tumor control or regression in 80% to 85% of patients (Crawford 1989, Scher 1993, Small 1995, Schellhammer 1997). Despite hormonal therapy, virtually all patients with metastatic prostate cancer ultimately develop progressive disease (Small 1997, Scher 1996). Management of androgen independent prostate cancer is a significant clinical challenge. Currently, the choices for patients whose first-line hormonal therapy has failed include the following:

1. No Treatment. Because there is no standard of care for these patients, many patients who are asymptomatic or minimally symptomatic may be simply monitored. When symptoms develop or increase, they may be treated with prescription analgesics, including opioids, or palliative chemotherapy or local radiation.
2. Secondary Hormone Therapy. Secondary hormonal maneuvers, such as antiandrogen addition or withdrawal, ketoconazole, aminoglutethimide, megestrol acetate, or corticosteroids may produce PSA responses in some patients, but have not been demonstrated to prolong survival.
3. Standard and Experimental Chemotherapy. Chemotherapy, either single agent or in combination, has resulted in objective response rates of 15% to 30% and is palliative for symptomatic patients. In October 2000, mitoxantrone (Novantrone<sup>®</sup>) in combination with corticosteroids was approved for use in symptomatic advanced prostate cancer based on improved palliative responses compared to corticosteroids alone (Tannock 1996). In May 2004, docetaxel (Taxotere<sup>®</sup>) was approved for use in combination with prednisone for the treatment of patients with metastatic androgen independent prostatic carcinoma, and was shown to confer a median survival benefit of 2.4 months when compared to mitoxantrone plus prednisone (Tannock 2004). These chemotherapeutic agents are associated with toxicities, which may include immunosuppression, neutropenia, anemia, nausea, fatigue, fluid retention, skin and nail changes, and peripheral neuropathy.

The development of new agents for the treatment of androgen independent prostate cancer is urgently needed. The current trial evaluates a new approach to prostate cancer treatment using autologous APCs loaded with a recombinant antigen, comprised of PAP fused to human GM-CSF.

## **2.2 Pre-Clinical Studies**

Pre-clinical studies in rats demonstrated that APCs loaded with a fusion protein consisting of rat prostatic acid phosphatase (rPAP) coupled to a targeting molecule, rat granulocyte-macrophage colony-stimulating factor (rGM-CSF), induced strong cellular immune responses in vivo to tissues and tumors that express PAP (Laus 2001). Based on these observations, an APC product, designated APC8015 (sipuleucel-T), was developed for the treatment of men with prostate cancer.

## **2.3 Previous Human Experience**

Separate Phase 1 and Phase 2 trials of sipuleucel-T were performed at the University of California, San Francisco (UCSF) (Small 2000) and the Mayo Clinic (Burch 2000, Burch 2004). Data from the Phase 1 and Phase 2 trials demonstrated that intravenous infusions of sipuleucel-T were generally well tolerated and effectively stimulated T cell responses to the immunogen. In addition, following therapy with sipuleucel-T, several subjects had decreases in PSA levels or objective tumor regressions suggesting anti-tumor activity. A dose of 3 million CD54<sup>+</sup> cells was adequate to generate an immune response. There were no apparent dose related or dose limiting toxicities, warranting the conclusion that the maximum cell dose that could be manufactured from a single leukapheresis product was safe.

A randomized, placebo-controlled, Phase 3 trial (D9901, n = 127 subjects) was subsequently conducted. A statistically significant survival benefit was demonstrated, with the relative risk of death 70% greater for subjects randomized to placebo ( $P = 0.010$ , 2-sided log rank; HR = 1.71). The median survival was 25.9 months for subjects randomized to sipuleucel-T compared to 21.4 months for those randomized to placebo. At 36 months from randomization, the survival rate for subjects receiving sipuleucel-T was 3.1 times higher than the survival rate for subjects receiving placebo (34% vs. 11%;  $P = 0.0046$ , chi square) (Small 2006). In addition, when the Kaplan-Meier curves for time to disease progression were compared, there was a delay in the time from randomization to disease progression in the sipuleucel-T group compared with the placebo group (HR = 1.45 [95% CI: 0.99, 2.11],  $P = 0.052$ ). A second smaller, randomized, placebo-controlled Phase 3 trial (D9902A, n = 98 subjects) with the same design as D9901 demonstrated a 20% improvement in median survival for subjects who were randomized to receive sipuleucel-T compared to placebo. Furthermore, at the 3-year follow-up, the percentage of subjects alive in the sipuleucel-T treated group was substantially greater than the percentage of subjects alive who received placebo. The results from this study did not reach statistical significance based on the log rank test. A secondary analysis using a Cox multivariable regression analysis of overall survival, which adjusted for prognostic factors known to influence survival, met the criteria for

statistical significance. The HR observed in this Cox multivariable regression analysis was similar to that seen using the same analysis in D9901.

The overall AE profile observed in Phase 3 studies (D9901 and D9902A) was similar to that observed in the Phase 2 studies, although infusion-related fevers and rigors appeared to be more common. The following infusion-related AEs occurred more frequently ( $P \leq 0.05$ ) in subjects treated with sipuleucel-T than those treated with placebo: chills, pyrexia, headache, asthenia, dyspnea, vomiting, and tremor. However, these events generally resolved within 1 to 2 days.

The sipuleucel-T Investigator's Brochure contains a comprehensive review of previous clinical experience and product safety.

## **2.4 Rationale**

Results from studies D9901 and D9902A provide evidence that sipuleucel-T prolongs survival in subjects with metastatic androgen independent prostatic adenocarcinoma. The current protocol (D9902B) is designed to provide additional clinical data in this patient population with survival as the defined primary endpoint.

Time to objective disease progression will be a secondary endpoint in this study. In study D9901, there was a benefit for time to disease progression. In this trial, the sample size will be larger than in study D9901 and the imaging studies more frequent. This will increase the probability of demonstrating a delay in time to objective disease progression.

Because objective disease progression is strictly limited to radiographic progression in this protocol, clinical progression will also be assessed as a tertiary endpoint.

PSADT and immune response will be evaluated to determine any differences in these measurements between the 2 treatment arms, and to explore correlations with clinical outcomes. Establishing these measurements as possible surrogates for clinical outcomes could prove valuable for the validation of future product improvements.

## **3.0 STUDY OBJECTIVES**

### **3.1 Efficacy Objectives**

#### **3.1.1 Primary Efficacy Objective**

To assess the efficacy of sipuleucel-T in prolonging survival of subjects with metastatic androgen independent prostate cancer.

#### **3.1.2 Secondary Efficacy Objective**

To assess the efficacy of sipuleucel-T in delaying time to objective disease progression in subjects with metastatic androgen independent prostate cancer.

### 3.1.3 Tertiary Efficacy Objective

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

## 3.2 Safety Objective

To compare AEs, laboratory evaluations, and vital sign measurements between the 2 treatment groups.

## 4.0 PRODUCT INFORMATION

### 4.1 PA2024

PA2024 is a recombinant fusion protein consisting of human PAP and GM-CSF. GM-CSF acts as a targeting molecule that directs the PAP antigen to APCs and promotes antigen uptake and processing. PAP is a tissue-specific target antigen rather than a tumor-specific target antigen. Studies with specific monoclonal antibodies and RNA probes indicate that the antigen is strictly prostate-specific. Immunohistochemical studies reveal that the antigen is expressed by normal prostate tissue, and > 90% of all prostatic adenocarcinomas, but is not expressed by other tissues (Goldstein 2002). PAP is secreted by the prostate tumor cells in vivo, and an elevated serum level is found in most subjects with advanced prostate cancer (Kuriyama 1982).

The cDNA for PAP has been isolated. Analysis of sequence homology with other known proteins reveals a low risk of cross-reactivity of immune responses.

GM-CSF is a multilineage factor that may also activate mature granulocytes and macrophages, and may activate quiescent APCs.

### 4.2 Preparation of sipuleucel-T and placebo

Further information regarding the manufacture and characterization of sipuleucel-T and placebo is provided in the sipuleucel-T Investigator's Brochure.

#### 4.2.1 Leukapheresis and Collection of Quiescent APCs

Collection of blood cells to generate sipuleucel-T is analogous to that for autologous blood transfusions. Briefly, subjects undergo a standard 1.5 to 2.0 blood volume leukapheresis to harvest peripheral blood mononuclear cells (PBMCs; primarily lymphocytes and monocytes). Prior mobilization with a colony-stimulating factor is not performed. Immediately after collection, the leukapheresis product is transported to a regional manufacturing facility.

#### 4.2.2 Sipuleucel-T

Sipuleucel-T is an autologous cell product consisting of APCs loaded with prostate antigen PA2024. Preparation of sipuleucel-T entails isolating quiescent APCs from a subject's peripheral blood leukapheresis product by buoyant density techniques and then culturing them

for approximately 2 days in the presence of PA2024. The culture medium does not contain serum or exogenous cytokines. During the culture process, APCs specifically and selectively pick up antigen (PA2024) and differentiate into antigen loaded APCs capable of presenting antigen to T cells. These APCs thus represent the cells responsible for the biological activity of sipuleucel-T. Other cell populations in sipuleucel-T co-purify with APCs during buoyant density centrifugation, but do not incorporate or present antigen, and are therefore referred to as “non-APCs.” After the culture period, the cells are washed and suspended in Lactated Ringer’s Injection, USP. The final preparation of PA2024-loaded APCs is designated sipuleucel-T. Sipuleucel-T is placed in a refrigerated package and transported to the clinical site for infusion.

#### 4.2.3 Placebo

Placebo (APC-Placebo) is an autologous cell product consisting of APCs not loaded with antigen. To prepare placebo, one-third of the leukapheresis product is stored at 2°C to 8°C for approximately 2 days in the absence of antigen. The cells are then washed, suspended in Lactated Ringer’s Injection, USP, placed in a refrigerated package, and transported to the clinical site for infusion. The remainder (two-thirds of the original leukapheresis product) is cryopreserved and used later as the cell source for generating the PA2024-loaded APCs for subjects who meet the objective disease progression endpoint and subsequently enroll in trial PB01. In that trial, the cryopreserved quiescent APCs will be thawed, and the cells will be processed according to the procedures described above for preparing sipuleucel-T, resulting in the product APC8015F.

#### 4.2.4 Quality Testing

Quality control (QC) testing is performed at several time points during the manufacturing process and on samples of the final product. If the final product passes all required release tests, an approval to infuse the product (Cell Product Disposition Form) is faxed to the infusion center. If a cell product does not meet Dendreon quality specifications, Dendreon will contact the infusion center by telephone and by fax. Dendreon will provide instructions for product return or destruction of cell products that are not approved or not infused.

### 4.3 Storage and Time Limitations

The infusion of sipuleucel-T or placebo must begin prior to the expiration time indicated on the product label. Expired cell products must not be infused.

### 4.4 Administration

Subjects are premedicated with acetaminophen and an antihistamine such as diphenhydramine prior to the infusion. After the site receives the Cell Product Disposition Form indicating the cell product is approved, the infusion is administered over approximately 60 minutes through an intravenous (IV) line suitable for blood transfusion (without a cell filter). Subjects are observed for at least 30 minutes following the infusion.

## 5.0 SELECTION OF STUDY POPULATION

Men at least 18 years of age with asymptomatic or minimally symptomatic, metastatic, androgen independent prostate cancer will be recruited for this study. Prior to the initiation of screening procedures, the purpose and procedures of the study will be explained to each subject, and each subject will then sign an Institutional Review Board (IRB) approved consent form. The subject will subsequently undergo screening assessments to determine if he meets the eligibility criteria for the study.

### 5.1 Inclusion Criteria

- 5.1.1 Written informed consent obtained prior to the initiation of study procedures.
- 5.1.2 Histologically documented adenocarcinoma of the prostate. A specimen of the primary tumor must be submitted to the central pathology lab prior to registration for confirmation of prostatic adenocarcinoma and for Gleason Sum regrading. In exceptional circumstances where the primary tumor has been disposed of, a pathology report with clearly documented primary Gleason score may be acceptable with prior Dendreon approval.
- 5.1.3 Metastatic disease as evidenced by soft tissue and/or bony metastases on baseline bone scan and/or computed tomography (CT) scan of the abdomen and pelvis. Subjects whose metastatic disease is detectable only on chest CT scan are not eligible.
- 5.1.4 Androgen independent prostatic adenocarcinoma. Subjects must have current or historical evidence of disease progression concomitant with surgical or medical castration, as demonstrated by PSA progression OR progression of measurable disease OR progression of non-measurable disease as defined below:
  - 5.1.4.1 PSA: Two consecutive PSA values, at least 14 days apart, each  $\geq 5.0$  ng/mL and  $\geq 50\%$  above the minimum PSA observed during castration therapy or above the pre-treatment value if there was no response.
  - 5.1.4.2 Measurable disease (as defined in [Section 6.1.1](#)):  $\geq 50\%$  increase in the sum of the 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 the pre-castration measurements if there was no response.
  - 5.1.4.3 Non-measurable disease (as defined in [Section 6.1.2](#)).
    - 5.1.4.3.1 Soft tissue disease: The appearance of 1 or more new lesions, and/or unequivocal worsening of non-measurable disease when compared to imaging studies acquired during castration therapy or against the pre-castration studies if there was no response.

- 5.1.4.3.2 Bone disease: Appearance of 2 or more new areas of abnormal uptake on bone scan when compared to imaging studies acquired during castration therapy or against the pre-castration studies if there was no response. Increased uptake of pre-existing lesions on bone scan does not constitute progression.
- 5.1.5 Serum PSA  $\geq$  5.0 ng/mL.
- 5.1.6 Castration levels of testosterone (< 50 ng/dL) achieved via medical or surgical castration. Surgical castration must have occurred at least 3 months prior to registration. Subjects who are not surgically castrate must be receiving medical castration therapy, have initiated such therapy at least 3 months prior to registration, and continue such therapy until the time of confirmed objective disease progression.
- 5.1.7 Life expectancy of at least 6 months.
- 5.1.8 Men  $\geq$  18 years of age.
- 5.1.9 Adequate hematologic, renal, and liver function as evidenced by the following:
- |   |  |
|---|--|
| White blood cell (WBC)                  | $\geq$ 2,500 cells/ $\mu$ L            |
| Absolute neutrophil count (ANC)         | $\geq$ 1,000 cells/ $\mu$ L            |
| Platelet Count                          | $\geq$ 100,000 cells/ $\mu$ L          |
| Hemoglobin (Hgb)                        | $\geq$ 9.0 g/dL                        |
| Creatinine                              | $\leq$ 2.0 mg/dL                       |
| Total Bilirubin                         | $\leq$ 2 x upper limit of normal (ULN) |
| Aspartate aminotransaminase (AST, SGOT) | $\leq$ 2.5 x ULN                       |
| Alanine aminotransaminase (ALT, SGPT)   | $\leq$ 2.5 x ULN                       |
- 5.1.10 Negative serology tests for human immunodeficiency virus (HIV) 1 and 2, human T cell lymphotropic virus (HTLV)-1, and Hepatitis B and C.

## 5.2 Exclusion Criteria

- 5.2.1 The presence of lung, liver, or known brain metastases, malignant pleural effusions, or malignant ascites.
- 5.2.2 Moderate or severe symptomatic metastatic disease. Subjects who meet either of the following criteria must be excluded:
- 5.2.2.1 A requirement for treatment with opioid analgesics for any reason within 21 days prior to registration.
- 5.2.2.2 Average weekly pain score of 4 or more as reported on the 10-point Visual Analog Scale (VAS) on the Registration Pain Log.

5.2.3 Eastern Cooperative Oncology Group (ECOG) performance status  $\geq 2$  (see [Appendix 1](#)).

5.2.4 Use of non-steroidal antiandrogens (e.g., flutamide, nilutamide, or bicalutamide) 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  $\geq 4$  weeks (flutamide) or  $\geq 6$  weeks (bicalutamide, nilutamide) following antiandrogen discontinuation and prior to registration.

5.2.5 Treatment with chemotherapy within 6 months of registration, except as noted below.

Treatment with chemotherapy  $\geq 3$  months prior to registration is allowed provided that all of the following criteria are met:

5.2.5.1 The post-chemotherapy PSA is  $\geq$  the pre-chemotherapy PSA or the nadir PSA achieved during chemotherapy.

5.2.5.2 The post-chemotherapy bone scan is not improved in comparison to the pre-chemotherapy bone scan.

5.2.5.3 For subjects with nodal disease followed by CT or other imaging modality, the post-chemotherapy imaging study must not show a decrease in the size or number of pathologically enlarged lymph nodes in comparison to the pre-chemotherapy imaging study.

Additionally, subjects who received more than 2 chemotherapy regimens at any time prior to registration are excluded.

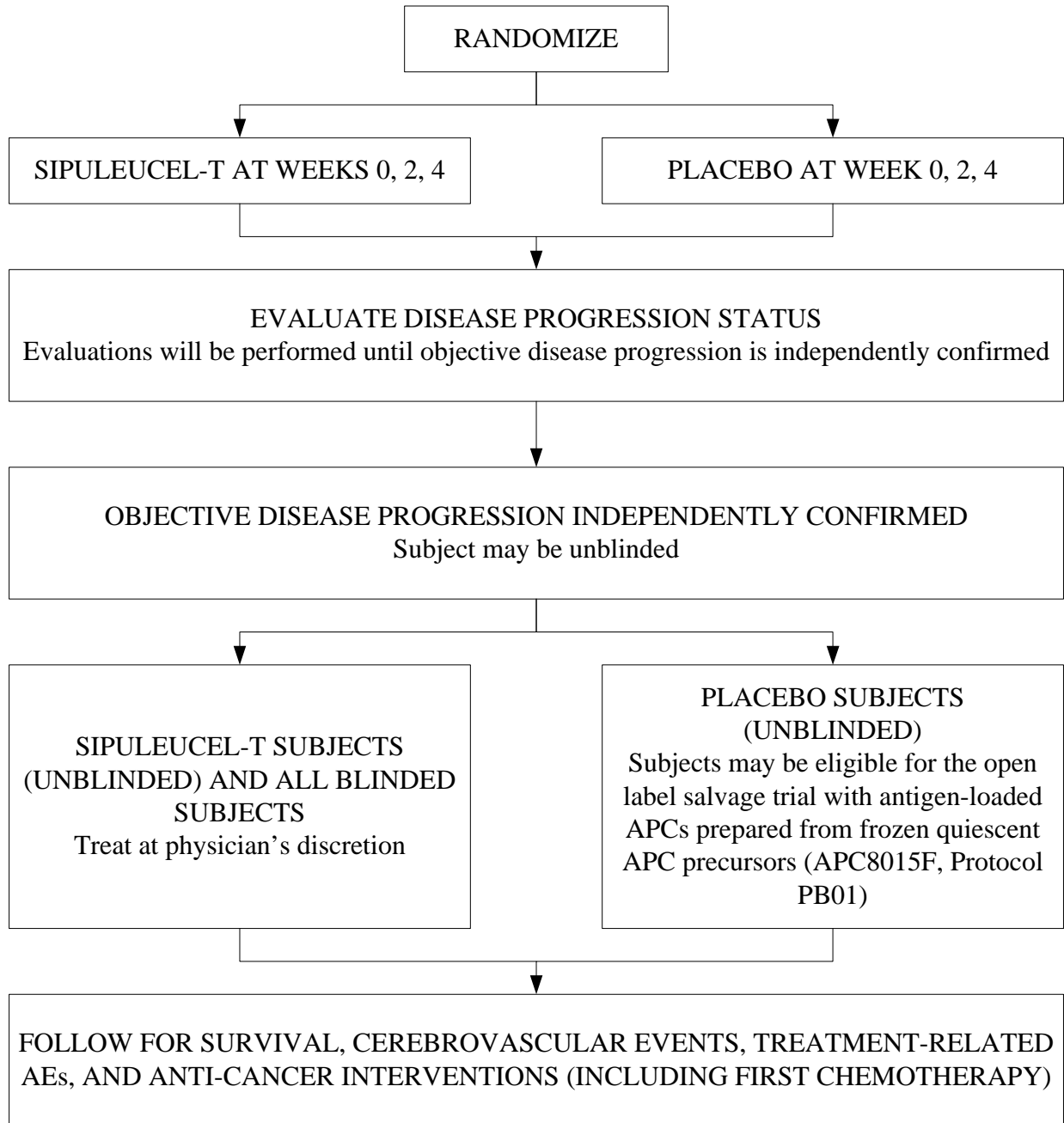
5.2.6 Initiation or discontinuation of bisphosphonate therapy within 28 days prior to registration. Subjects taking bisphosphonate medication must not have their dosing regimen altered until objective disease progression is independently confirmed.

5.2.7 Treatment with any of the following medications or interventions within 28 days of registration:

- Systemic corticosteroids. Use of inhaled, intranasal, and topical steroids is acceptable.

- External beam radiation therapy or surgery.
  - PC-SPES (or PC-SPEC) or saw palmetto.
  - Megestrol acetate (Megace<sup>®</sup>), diethyl stilbestrol (DES), or cyproterone acetate.
  - Ketoconazole.
  - 5- $\alpha$ -reductase inhibitors (e.g., finasteride [Proscar<sup>®</sup>], dutasteride [Avodart<sup>®</sup>]).
  - High dose calcitriol [1,25(OH)<sub>2</sub>VitD] (i.e., > 7.0  $\mu$ g/week).
  - Any other systemic therapy for prostate cancer (except for medical castration).
- 5.2.8 Treatment with any investigational vaccine within 2 years of registration or treatment with any other investigational product within 28 days of registration.
- 5.2.9 Participation in any previous study involving sipuleucel-T, regardless whether the subject received sipuleucel-T or placebo.
- 5.2.10 Pathologic long-bone fractures, imminent pathologic long-bone fracture (cortical erosion on radiography > 50%) or spinal cord compression.
- 5.2.11 Paget's disease of bone.
- 5.2.12 A history of 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  $\geq 3$  years at the time of registration.
- 5.2.13 A requirement for systemic immunosuppressive therapy for any reason.
- 5.2.14 Any infection requiring parenteral antibiotic therapy or causing fever (temperature > 100.5°F or 38.1°C) within 1 week prior to registration.
- 5.2.15 A known allergy, intolerance, or medical contraindication to receiving the contrast dye required for the protocol-specified CT imaging.
- 5.2.16 Any medical intervention or other condition which, in the opinion of the Principal Investigator or the Dendreon Medical Monitor, could compromise adherence with study requirements or otherwise compromise the study's objectives.

**Figure 1 Overall Schema**



## 6.0 CRITERIA FOR EVALUATION AND CLINICAL ENDPOINT DEFINITIONS

### 6.1 Criteria for Evaluation

To ensure comparability, baseline and all subsequent bone scans and CTs must be obtained according to the procedures outlined in the Imaging Manual.

#### 6.1.1 Measurable Disease

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

#### 6.1.2 Non-Measurable Disease

6.1.2.1 All other soft tissue lesions, including small lesions (at least 1 diameter  $< 2.0$  cm on CT or MR<sup>§§</sup>), 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.

6.1.2.2 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.

#### 6.1.3 Index Lesions

At baseline, the radiologist will select all measurable lesions up to a maximum of 8 lesions in total. If there are no measurable lesions, non-measurable lesions may be chosen as index lesions.

Index lesions should be selected on the basis of their size (lesions with the longest diameters), their suitability for accurate repeated measurements by imaging techniques, and how representative they are of the subject's tumor burden.

Index lesions will be measured with the size estimated by cross product of the longest diameter and the greatest perpendicular diameter. The sum of the products (SOP) of diameters of all index lesions will be calculated and reported for each time point.

#### 6.1.4 Non-Index Lesions

All other soft tissue lesions should be identified and documented. The presence, absence, or unequivocal progression of any non-index lesion should be noted throughout follow-up.

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\* Serial images obtained via MR may be used to evaluate androgen independence prior to registration, but may not be used to stage subjects at baseline or for restaging and assessing disease progression.

Non-index measurable lesions may be measured at the discretion of the reader as an aid to document unequivocal progression, but will not be used in calculation of the SOP of index lesions.

#### 6.1.5 Bone Lesions

All bone lesions, regardless of number, will be identified on nuclear medicine bone scans at baseline and assessed at each follow-up visit.

## 6.2 Clinical Endpoint Definitions

### 6.2.1 Survival

Survival is the time from randomization until death due to any cause.

### 6.2.2 Objective Disease Progression

All objective disease progression events must be confirmed by the central imaging review facility as outlined in the Independent Radiology Review Committee (IRRC) Charter. All references in this protocol to independently confirmed objective disease progression refer to confirmation by the IRRC, not by a local radiologist.

*Any of the following constitute objective disease progression (WHO 1979, Hussain 2000):*

#### 6.2.2.1 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.

#### 6.2.2.2 Non-Index Lesions

The appearance of 1 or more new lesions and/or unequivocal progression of existing non-index lesions. Worsening or new effusions or ascites will not be considered radiologic progression.

#### 6.2.2.3 Bone Disease

An appearance of  $\geq 2$  new areas of abnormal uptake on bone scan. Increased uptake of pre-existing lesions on bone scan does not constitute progression.

The appearance of a new pathologic fracture or new spinal cord compression constitutes progression.

### 6.2.3 Response

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  $\geq$  4 weeks later (WHO 1979, Hussain 2000).

#### 6.2.3.1 Complete Response

Disappearance of all index, non-index, and bone lesions confirmed by a repeat consecutive assessment no less than 4 weeks after the criteria for complete response (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 partial response (PR).

#### 6.2.3.2 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 4 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.

#### 6.2.3.3 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 (SD) criteria at least once no less than 5 weeks after the first investigational product infusion.

#### 6.2.4 Clinically Significant Disease-Specific Events

Events that cannot be confirmed on serial imaging studies, and therefore do not constitute objective disease progression as defined by this protocol, but are nevertheless clinically significant events related to progressive prostate cancer, include development of the following:

6.2.4.1 Spinal cord or nerve root compression, if not confirmed by serial imaging studies.

6.2.4.2 Pathologic fracture, if not confirmed by serial imaging studies.

6.2.4.3 Metastatic disease in an anatomy for which no baseline scan is available for comparison to allow documentation of interval change on serial imaging studies.

- 6.2.4.4 Progressive disease (as defined in [Section 6.2.2](#)) in an anatomy for which there is a baseline imaging assessment but serial imaging has not been performed (e.g., mediastinal or lung metastases).
- 6.2.4.5 A clinical indication for radiation therapy.
- 6.2.4.6 At least 2 of the following clinical signs/symptoms in comparison to baseline:
- An increase in ECOG performance status of  $\geq 1$  grade.
  - Progressive anemia, defined as either (i) a decrease in hemoglobin of  $\geq 2$  g/dL **and** to a level below the lower limit of normal in the central lab reference range, **or** (ii) a requirement for therapy with a hematopoietic growth factor (e.g., Procrit<sup>®</sup>) 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.

#### 6.2.5 Clinical Progression

Clinical progression is the first occurrence of either of the following:

- Objective disease progression ([Section 6.2.2](#))
- Development of clinically significant disease-related events ([Section 6.2.4](#)). If the subject experiences 2 or more of the events noted in [Section 6.2.4.6](#), the date of the disease-related event is the date the first event of the 2 (or more) is documented.

#### 6.2.6 PSA Doubling Time

PSA doubling time will be calculated as described in [Section 7.6.1.3](#).

#### 6.2.7 Immune Response

Evaluation of the immune response will focus on humoral and cellular responses specific for the immunizing antigen (PA2024) in addition to prostate tissue and tumor associated antigens. Both serum and PBMCs obtained at the indicated time points will be cryopreserved and all samples from a single individual will be evaluated in the same assay.

Serum antibody titers will be determined by enzyme-linked immunosorbent assay (ELISA). Antibody isotypes may be determined for some individuals.

For proliferation assays, peripheral blood lymphocytes will be incubated with increasing concentrations of antigen (PA2024), pulsed with <sup>3</sup>H thymidine, and the radioactivity incorporated into proliferating cells determined.

The frequency of antigen specific, cytokine producing cells will be determined by an enzyme-linked immunospot (ELISPOT) assay. Primary analysis will focus on interferon gamma producing cells, although other cytokines may also be evaluated. ELISPOT assays may use whole PBMC, or CD4<sup>+</sup> and CD8<sup>+</sup> cells as responding cells.

Additional exploratory analyses may include isolation and characterization of antigen specific T cell clones, evaluation of antigen specific T cell populations by spectratyping T cell receptor expression, characterization of antigen response by cytokine, and chemokine production.

Small aliquots from the cell product may be obtained for assays which may include, but will not be limited to: characterization of cells by flow cytometry, demonstration of antigen presenting capacity, evaluation of cytokines produced during cell culture, and characterization of gene expression changes using microarray analysis.

No genetic analyses will be performed except for HLA typing.

## **7.0 STATISTICAL CONSIDERATIONS**

### **7.1 Study Design**

Protocol D9902 is divided into 2 parts, D9902A and D9902B. D9902A enrolled subjects under the original protocol (17 NOV 1999) and through Amendment 4 (12 MAR 2001). Its targeted study population was subjects with asymptomatic, metastatic, androgen independent prostate cancer regardless of Gleason sum. Time to objective disease progression was the primary endpoint and time to onset of disease-related pain a secondary endpoint. However, for the final analysis of D9902A, the secondary endpoint was changed to survival in an amendment to the statistical analysis plan before the trial was unblinded.

Enrollment into study D9902B began with Amendment 5 (21 MAY 2003). Under this amendment, the criteria for the study population were modified to include only subjects with Gleason Sum  $\leq 7$  malignancies. Amendment 7 (11 OCT 2005) further modified the targeted study population to include subjects with asymptomatic or minimally symptomatic disease regardless of Gleason Sum. Survival is the primary endpoint and time to objective disease progression a secondary endpoint. Study D9902B is a prospective, randomized, double blind, placebo-controlled Phase 3 trial designed to evaluate the safety and efficacy of APC8015 for the treatment of metastatic androgen independent prostate cancer in subjects who are asymptomatic or minimally symptomatic. It is designed to be a stand alone study and as such will be analyzed and reported separately from D9902A.

An open label salvage therapy trial (Protocol PB01) is available to eligible subjects who are unblinded after developing objective disease progression and are determined to be in the placebo arm.

## **7.2 Randomization**

Subjects will be allocated to either sipuleucel-T or placebo using Pocock and Simons' minimization method (Pocock 1975). The allocation process will minimize the degree of imbalance between the 2 treatment groups for primary Gleason grade ( $\leq 3$ ,  $\geq 4$ ), the number of bone metastases (0 to 5, 6 to 10,  $>10$ ), and bisphosphonate use (yes, no) across treatment groups. Imbalance between treatment groups will be assessed using the deterministic variance method (Pocock 1975).

## **7.3 Efficacy Objectives**

### **7.3.1 Primary: Overall Survival**

To assess the efficacy of sipuleucel-T in prolonging the survival of subjects with metastatic androgen independent prostate cancer.

### **7.3.2 Secondary: Time to Objective Disease Progression**

To assess the efficacy of sipuleucel-T in delaying objective disease progression in subjects with metastatic androgen independent prostate cancer.

### **7.3.3 Tertiary**

To assess the effect of sipuleucel-T in delaying clinical progression, increasing the prostate-specific antigen (PSA) doubling time (PSADT), and generating an immune response.

## **7.4 Safety**

The following data will be analyzed as part of the evaluation of safety:

- Adverse events
- Laboratory data
- Vital sign data
- Clinically significant disease-specific events

## **7.5 Other**

- Demographic and baseline characteristics
- Subject disposition
- Concomitant medications and procedures
- Study treatment administration

- Anti-cancer therapies

## 7.6 Statistical Methods

### 7.6.1 Efficacy

All efficacy analyses will compare sipuleucel-T to placebo. Unless otherwise specified, the statistical tests are based on the superiority hypothesis. One interim analysis is planned for this study based on the O'Brien-Fleming spending function. The details of the interim analysis and levels of significance are provided in Protocol D9902B Statistical Analysis Plan.

#### 7.6.1.1 Primary Efficacy Variable: Overall Survival

Overall survival (OS) is defined as the time from randomization to death due to any cause. Those subjects alive at the time of analysis will be censored in the analysis at the day of their last documented study evaluation date or contact date, whichever is later. In addition, subjects will be censored at the date of their last documented study evaluation or contact date, whichever is later, if they prematurely discontinue from the study (e.g., are lost to follow up or have withdrawn consent) and their survival status cannot be verified at the time of analysis.

Overall survival time will be calculated as follows:

- For subjects who died
  - Survival time (days) = [(death date) – (randomization date)] + 1
- For subjects who are censored
  - Survival time (days) = [(maximum(last study visit, last contact date)) – (randomization date)] + 1

For OS data, the primary test (Wald's test) is based on the stratified Cox regression model adjusted for 2 covariates (PSA [natural log (ln)] and lactate dehydrogenase [LDH, ln]). The primary model will include the treatment factor and all stratification variables [primary Gleason grade ( $\leq 3$ ,  $\geq 4$ ), number of bone metastases (0 – 5, 6 – 10, >10), and bisphosphonate use (yes, no)] and 2 covariates (PSA [ln] and LDH [ln]). Missing covariates will be imputed by the median of the data collected from subjects without any missing values. An analysis based only on subjects without any missing baseline covariates (PSA and LDH) will be conducted to support the primary analysis.

The estimated HR of the treatment effect and its 2-sided, 95% confidence interval (CI), using the placebo arm as the denominator, will be generated based on the same Cox regression model described above. The Kaplan-Meier method will be used to estimate the overall survival distribution.

To support the primary analysis, the p-value associated with the log rank test stratified by primary Gleason grade ( $\leq 3$ ,  $\geq 4$ ), number of bone metastases (0 – 5, 6 – 10, >10), and bisphosphonate use (yes, no), as well as the hazard ratio (with its 95% confidence interval) derived from the stratified but unadjusted Cox regression model, will be provided.

Additional OS analyses may be conducted if there are more than 304 death events in the final database to support the primary analysis.

One interim OS analysis is planned when approximately 228 death events (75% of the total number of death events) have been observed. The difference in OS between treatment groups is considered statistically significant if the 2-sided p-value associated with the primary model for the interim or the final analysis is less than the pre-specified significance level allocated to the analysis based on the O'Brien-Fleming alpha spending function (O'Brien 1979).

#### 7.6.1.2 Secondary Efficacy Variable: Time to Objective Disease Progression

Time to objective disease progression (TTP) is defined as the time from randomization to achieving objective disease progression, as determined by the Independent Radiology Review Committee (IRRC) for the study. Subjects who have not demonstrated objective disease progression prior to the analysis of objective disease progression will be censored at the time of their last imaging study obtained per protocol. Non-protocol specified imaging studies such as MRI scans, ultrasound exams, and x-rays will not be included in this analysis. Subjects who have been lost to follow-up, have withdrawn consent, or have discontinued follow-up prior to confirmed objective disease progression will also be censored at the date of their last imaging study.

Time to disease progression will be calculated as follows:

- For subjects with objective progression
  - TTP (days) = [(IRRC date of objective disease progression) – (randomization date)] + 1
- For subjects who are censored
  - TTP (days) = [(last imaging study date) – (randomization date)] + 1

The IRRC will provide the date of objective disease progression. If the progression event cannot be determined by IRRC reviewers, the subject will be considered without objective disease progression and will be censored at the date of their last imaging study. A death event prior to objective disease progression will be analyzed as a competing event.

The 2-sided p-value associated with the treatment effect using the log rank test stratified by primary Gleason grade ( $\leq 3$ ,  $\geq 4$ ), number of bone metastases (0 – 5, 6 – 10, >10), and bisphosphonate use (yes, no) will be provided to assess the treatment effect. The stratified unadjusted Cox regression model will be applied to assess the HR and its 95% CI. This model

will not be adjusted for any covariates. The TTP distribution will be constructed based on the cumulative incidence method.

### 7.6.1.3 Tertiary Efficacy Variables

#### Time to Clinical Progression

Time to clinical progression (TTCP) will be calculated as the time from randomization to clinical disease progression (defined in [Section 6.2.5](#)). Subjects who have not demonstrated clinical disease progression prior to the analysis of clinical disease progression will be censored at the time of their last clinical assessment (i.e., clinical study visit or imaging study, whichever occurs later). A death event prior to clinical progression will be analyzed as a competing event.

Time to clinical progression will be calculated as follows:

- For subjects with clinical disease progression
  - TTCP (days) = [(clinical disease progression date – (randomization date)] + 1
- For subjects who are censored
  - TTCP (days) = [(maximum (last clinical assessment date, last imaging study date)) – (randomization date)] + 1

Statistical methods that are used to analyze TTP will also be applied to TTCP.

#### PSA Doubling Time

The population PSA time slope (or PSA velocity) for each treatment arm will be computed based on a mixed effects model (Svatek 2006) with all PSA measurements from baseline until the institution of other systematic anticancer therapy. The response variable is the log transformed PSA. The fixed effects will include stratification factors, time (as a continuous variable), treatment, and treatment by time interaction. Subject will be considered as a random effect. The p-value that is associated with the treatment effect will be used to evaluate PSADT. The estimated PSADT and its 2-sided 95% CI for each treatment arm will be computed using the estimated population slope for PSA (ln) based on the following formula:

$$\text{PSADT} = \frac{\ln(2)}{\text{Population Slope of the Regression Line for PSA (ln) Versus Time}}$$

In addition, a mixed effects model that can estimate both pre- and post-randomization PSA (ln) slopes will be examined.

#### Immune Response

Immune monitoring will be performed at baseline and Weeks 6, 14, and 26. (If a subject experiences objective disease progression prior to Week 26, a sample will be obtained 2 months

after objective disease progression.) For each time point, a T cell stimulation index will be calculated as the median proliferation of triplicate wells with antigen divided by the median proliferation with cells only (no added antigen).

To determine whether sipuleucel-T induced an antigen specific cellular immune response greater than that induced by placebo, a repeated measurement mixed model approach for a log-transformed stimulation index will be evaluated. The model will include the treatment effect, visit, treatment by visit interaction, and subject (as a random effect). The immune response at each post-baseline visit will be compared between treatment groups or to baseline using a contrast statement.

In addition, the ratio of the stimulation index for the proliferation assays will be calculated for each subject as follows:

$$\text{Ratio} = \frac{\text{Post-Treatment Stimulation Index}}{\text{Pre-Treatment Stimulation Index}}$$

The Wilcoxon rank sum test will be used to compare the 2 treatment groups at each scheduled visit.

## 7.6.2 Safety

All safety analyses will compare sipuleucel-T to placebo.

### 7.6.2.1 Adverse Events

Adverse events (AEs) will be summarized and listed by treatment group and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term within each system organ class.

Summaries to be produced include the following:

- Incidence within system organ class (MedDRA);
- Incidence by decreasing frequency;
- Incidence by National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE, Version 3.0) severity grade, by decreasing frequency;
- Incidence of Grade 3 and Grade 4 AEs by decreasing frequency;
- Incidence of AEs that may have led to premature discontinuation of study therapy or withdrawal of consent.

Adverse events that occur multiple times for a subject will be counted only once per subject in incidence summary tables. In tables that enumerate AEs by severity, only the worst severity for an AE occurring multiple times for a subject will be counted.

No formal statistical testing is planned for the above AE summaries. A 2-sided Fisher’s exact test may be used to assess any potential trend, if appropriate. The p-values associated with the test will not be used for hypothesis testing.

Cerebrovascular events will be summarized by treatment assignment. In addition, the cerebrovascular event data will be summarized for subjects who received sipuleucel-T only, placebo only (placebo subjects who did not receive APC8015F), and placebo/APC8015F (placebo subjects who crossed over to receive APC8015F), respectively. Person-year adjusted cerebrovascular event incidence rates will also be provided for each treatment group.

### 7.6.2.2 Laboratory Data

Summaries of laboratory data collected from baseline onward will include the following:

- Incidence of laboratory toxicities by NCI CTCAE;
- Summary statistics (mean, median, standard deviation, minimum, maximum) for laboratory values and their change from baseline by time point;
- Shift from baseline by follow-up time points.

Normalized laboratory values for time points will be categorized as low, normal, or high using the normal range for each laboratory test. Incidence tables will then pair baseline to a subsequent time point using the categorizations described in [Table 1](#) to create a matched pair.

$$\text{Normalized Value} = \frac{(\text{Laboratory Value} - \text{Lower Limit of Normal})}{(\text{Upper Limit of Normal} - \text{Lower Limit of Normal})}$$

**Table 1 Laboratory Shift Table**

		Time Point X		
		Low	Normal	High
Baseline	Low	n <sub>11</sub>	n <sub>12</sub>	n <sub>13</sub>
	Normal	n <sub>21</sub>	n <sub>22</sub>	n <sub>23</sub>
	High	n <sub>31</sub>	n <sub>23</sub>	n <sub>33</sub>
Low	= below lower limit of normal	→ normalized value < 0		
Normal	= between lower and upper limit of normal	→ 0 ≤ normalized value ≤ 1		
High	= above upper limit of normal	→ normalized value > 1		

### 7.6.2.3 Vital Signs

Vital sign data (blood pressure, heart rate, respiration rate, and body temperature) will be summarized descriptively for time points immediately before and after each treatment. No inferential statistics will be performed for these summaries.

### 7.6.2.4 Clinically Significant Disease-Specific Events

The frequency distribution of clinically significant disease-specific events will be summarized by treatment group for subjects who had clinical progression.

## 7.6.3 Other Data

### 7.6.3.1 Demographics and Baseline Characteristics

Descriptive statistics for demographic and baseline disease data will be provided for the intent-to-treat (ITT) population, as well as for each treatment group.

### 7.6.3.2 Disposition

Subject disposition will be summarized by treatment group for the ITT population. This summary will include, but will not be limited to, the following:

- Number of subjects randomized;
- Number of subjects who had at least 1 leukapheresis;
- Number of subjects infused;
- Number of subjects who prematurely discontinued treatment;
- Reason(s) for premature discontinuation of treatment;
- Number of subjects who prematurely discontinued the study (i.e., refused further study evaluations [with the possible exception of survival status]);
- Reason(s) for premature discontinuation from the study;
- Number of subjects who died;
- Cause of death summary;
- Number of subjects in the efficacy and safety analysis sets.

In addition, the number of subjects screened for the trial will be summarized based on the randomization database (a separate database from the clinical database).

### 7.6.3.3 Concomitant Medications and Procedures

Concomitant medications and procedures will be presented in data listings by treatment group based on coded terms using the World Health Organization dictionary “WHODRUG.” All subjects in the ITT population will be included.

#### 7.6.3.4 Study Treatment Administration

To evaluate the infusion success and failure rate over the course of the study, the following information will be summarized:

- a) Number of subjects who received a total of 1, 2, or 3 infusions;
- b) Number of subjects undergoing leukapheresis at Week 0, Week 2, and Week 4;
- c) Number of subjects infused at Week 0, Week 2, and Week 4;
- d) Number of subjects undergoing leukapheresis more than once for an infusion at Week 0, Week 2, or Week 4;
- e) Elapsed time between infusions;
- f) Elapsed time between randomization and first infusion.

Items A through D will be summarized by their frequency distribution and by treatment group. Items E and F will be summarized with descriptive statistics (mean, median, standard deviation, minimum, and maximum) by treatment group.

#### 7.6.3.5 Anticancer Therapies

The frequency distribution of the first anticancer therapy received following the confirmation of objective disease progression will be summarized by treatment group for the ITT population.

### 7.6.4 Analysis Sets

#### 7.6.4.1 Efficacy

The primary analysis set for efficacy will be the ITT analysis set. It will include all subjects randomized to study D9902B. Subjects will be evaluated by their randomized treatment assignment and their assigned stratification characteristics. The primary set of efficacy analyses will evaluate all efficacy variables based on this analysis set.

#### 7.6.4.2 Safety

The safety analysis set will include all randomized D9902B subjects who underwent at least 1 leukapheresis. All safety variables (adverse events, laboratory data, and vital signs data) will be analyzed based on this analysis set. Subjects will be evaluated by the actual treatment they received.

### 7.6.5 Interim Analysis

An interim analysis is planned for this study when approximately 228 death events (approximately 75% of the total number of death events) have been observed, with a total of

approximately 304 death events to be expected for the final analysis. Specific details regarding the interim analyses are presented in the D9902B Statistical Analysis Plan.

### **7.7 Sample Size Considerations**

Approximately 500 subjects will be enrolled and randomized in a 2:1 ratio to receive sipuleucel-T or placebo. The final survival analysis will be performed when approximately 304 death events have been observed. This sample size is sufficient to detect a HR for death of 0.69 (sipuleucel-T versus placebo) using the 2-sided log rank test with 88% power for the final analysis at an overall significance level of 0.05.

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**APPENDIX 1 ECOG PERFORMANCE STATUS CRITERIA**

	<b>Performance Criteria</b>	<b>Karnofsky Scale equivalent</b>
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	90-100
1	Symptoms but ambulatory. Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	70-80
2	In bed < 50% of the time. Ambulatory and capable of self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	50-60
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	30-40
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	10-20
5	Dead	0