A RANDOMIZED, OPEN-LABEL, PHASE 2 STUDY OF SIPULEUCEL-T WITH CONCURRENT VERSUS SEQUENTIAL ADMINISTRATION OF ENZALUTAMIDE IN MEN WITH METASTATIC CASTRATE-RESISTANT PROSTATE CANCER

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PROTOCOL SIGNATURE PAGE
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Original Protocol: 16 MAY 2013

By signing below, the principal investigator agrees to adhere to the protocol.

Investigator Name: _____

Title: _____

Address: _____

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Signature: _____

Date: _____

PROTOCOL SYNOPSIS

Protocol Title: A Randomized, Open-label, Phase 2 Study of Sipuleucel-T with Concurrent Versus Sequential Administration of Enzalutamide in Men with Metastatic Castrate-Resistant Prostate Cancer

Protocol Number: P12-2

Clinical Phase: 2

Investigational Product, Dosage Form, Route, and Dose Regimen: Sipuleucel-T (Provenge®) is an autologous cellular immunotherapy product designed to stimulate an immune response against prostate cancer. It consists of autologous peripheral blood mononuclear cells (PBMCs), including antigen presenting cells ([APCs], defined as large CD54-positive PBMCs) that have been activated in vitro with prostate antigen PA2024, a recombinant fusion protein composed of prostatic acid phosphatase (PAP) linked to granulocyte-macrophage colony-stimulating factor.

A dose of sipuleucel-T is prepared using PBMCs from a single leukapheresis procedure. A minimum of 50 million APCs (the biologically active component of sipuleucel-T) are administered via a single intravenous (IV) infusion. A complete treatment of sipuleucel-T will include 3 doses of autologous cells, infused at approximately 2-week intervals.

Sipuleucel-T is indicated for use in patients with asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer (mCRPC).

Enzalutamide is an androgen receptor inhibitor. It is indicated for the treatment of patients with mCRPC who have previously received docetaxel. The enzalutamide dose used in this study will be 160 mg orally once daily.

Reference Product, Dosage Form, Route, and Dose Regimen: No reference product will be used in this clinical study.

Primary Objective:

To evaluate peripheral PA2024-specific T cell immune response to sipuleucel-T over time via a T cell stimulation index from a proliferation assay.

Secondary Objectives:

- To evaluate time to prostate-specific antigen (PSA) progression.

- To estimate the percent of subjects who are PSA progression-free at 12 months.
- To evaluate overall survival.
- To determine the magnitude of peripheral immune response over time as determined by the following:
  - Peripheral PAP-specific T cell immune response to sipuleucel-T over time via a T cell stimulation index from a proliferation assay.
  - T cell interferon-γ enzyme-linked immunosorbent spot assay (ELISPOT) response to PA2024 and PAP.
  - Humoral response to PA2024 and PAP by enzyme-linked immunosorbent assay (ELISA).
  - Chemokine and cytokine production via fluorescent immunoassay (Luminex® assay).
- To evaluate safety.

Exploratory Objectives:

- To evaluate time to next anticancer intervention.
- To evaluate time to first cancer-related opioid use.
- To evaluate time to Eastern Cooperative Oncology Group (ECOG) performance status decline.

Study Design and Duration:

This is a randomized, open-label study designed to assess the effects of sipuleucel-T when administered concurrently or sequentially with enzalutamide. This study consists of 3 phases. The screening phase will begin at the completion of the informed consent process and continue through registration. The active phase will begin at registration and continue through the post-treatment visit (30 to 37 days following the last study treatment). The long term follow-up (LTFU) phase will begin after the post-treatment visit and will continue until the subject's death or until Dendreon terminates the study.

Eligible subjects will be registered and randomly assigned in a 1:1 ratio to receive 3 infusions of sipuleucel-T in addition to a total of 52 weeks of concurrent or sequential treatment with enzalutamide. Subjects will be stratified by screening PSA levels (≥ 25 ng/mL, yes or no) and

screening lactate dehydrogenase (LDH) levels (≥ 200 IU/L, yes or no), both obtained from the central laboratory.

Enzalutamide treatment will occur either concurrently with sipuleucel-T (concurrent arm), or following administration of sipuleucel-T (sequential arm):

Concurrent Arm

Subjects will receive sipuleucel-T concurrently with enzalutamide (160 mg orally once daily). Enzalutamide treatment will start 2 weeks prior to the first leukapheresis and continue for 52 weeks or until disease progression or unacceptable toxicity, whichever occurs first. Subjects randomized to the concurrent arm who receive the 2-week enzalutamide run-in, but do not subsequently receive at least one partial (> 0 mL) infusion of sipuleucel-T will not receive any additional enzalutamide treatment, will undergo a post-treatment visit, and will enter the LTFU phase.

Sequential Arm

Subjects will receive sipuleucel-T followed by enzalutamide (160 mg orally once daily). Enzalutamide treatment will start approximately 10 weeks after the first infusion of sipuleucel-T and continue for 52 weeks or until disease progression or unacceptable toxicity, whichever occurs first. Subjects randomized to the sequential arm who do not receive at least one partial (> 0 mL) infusion of sipuleucel-T will not receive any enzalutamide treatment, will undergo a post-treatment visit, and will enter the LTFU phase.

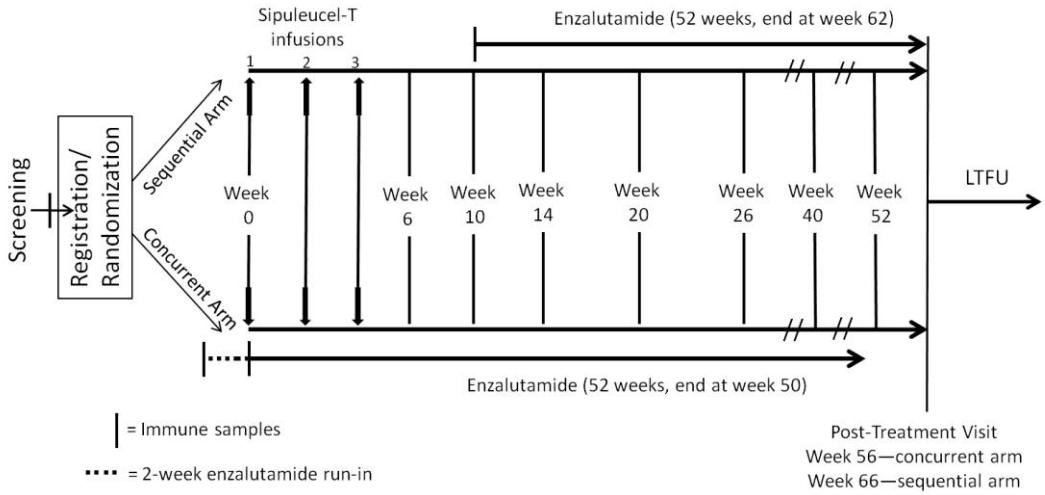
After 52 weeks of enzalutamide treatment provided by Dendreon, subjects in either treatment arm may continue to receive enzalutamide obtained from other sources at the discretion of their treating physician. Dendreon cannot provide enzalutamide beyond the protocol-specified duration of 52 weeks.

During the active phase, subjects in both arms will undergo a standard 1.5 to 2.0 blood volume leukapheresis, followed approximately 3 days later by an IV infusion of sipuleucel-T. This process will occur a total of 3 times at approximately 2-week intervals, as shown in the study design below. Immune monitoring blood samples will be drawn and clinical and safety assessments will be performed at screening, preleukapheresis visits 2 and 3, and weeks 6, 10, 14, 20, 26, 40 and 52, with the timing of visits based on the date of the first sipuleucel-T infusion. Immune monitoring blood samples will also be drawn following each sipuleucel-T infusion. Additional assessments including physical examinations, vital signs, ECOG performance status, AE monitoring, anticancer therapies, first opioid use for cancer-related pain, laboratory tests

(e.g., hematology and serum chemistries), and PSA monitoring will be performed at scheduled times.

During the LTFU phase, safety (treatment-related AEs, cerebrovascular events, and seizures), survival status, PSA, ECOG performance status, first opioid use for cancer-related pain (if applicable), and anticancer therapies will be assessed every 3 months until the subject's death or until Dendreon terminates the study.

The study design is illustrated below.



Abbreviation: LTFU = long-term follow-up.

Study Population and Sample Size: Approximately 100 men with mCRPC, 18 years of age or older will be enrolled.

Statistical Considerations:

The study is designed to test the null hypothesis of no difference between the treatment arms for immune response over time evaluated on the basis of PA2024-stimulated T cell proliferation via tritiated-thymidine uptake. The immune response population will consist of all subjects who receive 3 infusions of sipuleucel-T and at least 10 weeks of enzalutamide. PA2024-specific T cell proliferation responses over time will be compared between the concurrent arm and sequential arm using a repeated measurement mixed model analysis.

With 43 subjects per treatment arm (concurrent and sequential), there is 90% power to detect a 2-fold difference in mean response between the arms at any time point assuming a coefficient of

variation of 1.25. To allow for drop-outs and subjects who may not receive 3 infusions of sipuleucel-T or at least 10 weeks of enzalutamide, approximately 50 subjects per arm will be enrolled.

The intent-to-treat population is defined as all randomized subjects, regardless of whether they receive treatment. Analysis of non-immune response efficacy endpoints will be performed using this analysis population.

The safety population will include all subjects who undergo at least 1 leukapheresis procedure or receive at least 1 dose of enzalutamide.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1.0 INTRODUCTION

1.1 Background and Rationale

1.1.1 Prostate Cancer

In 2012, prostate cancer was the most common solid tumor malignancy in men in the United States, comprising 29% of new cancer cases (241,740 new cancer cases). Approximately 80% of prostate cancer cases are diagnosed when the cancer is still confined to the primary site. An additional 12% are diagnosed when locally advanced, and a further 4% when the cancer has already metastasized (Howlader 2011). Prostate cancer-related deaths typically occur as a result of complications of metastatic disease, with an estimated 28,170 annual deaths in 2012 (Siegel 2012).

Treatment of localized prostate cancer typically has a curative intent and may include radical prostatectomy, radiotherapy, brachytherapy, high intensity focused ultrasound, cryotherapy, or hormone therapy. Watchful waiting or active surveillance may be employed where the risks of the treatment outweigh the benefits, taking into account the patient's age and general health status.

Although primary therapy effectively cures the majority of patients, disease does recur in approximately 20% to 40% of individuals, where an increased level of serum prostate specific antigen (PSA) may be considered to be evidence of biochemical failure and progression to advanced disease (Ward 2005).

In men with recurrent disease, the current standard of care for androgen-dependent, advanced prostate cancer is androgen deprivation therapy (ADT) using a luteinizing hormone-releasing hormone (LHRH) agonist, an LHRH antagonist, or bilateral orchiectomy, which results in similar, and initially high, anticancer activity, with response rates attaining 80%. A peripheral antiandrogen, such as flutamide or bicalutamide, is typically used during the initial treatment period with an LHRH agonist to block the transient testosterone flare, but randomized Phase 3 trials have not consistently demonstrated a survival benefit with continuous combined androgen blockade (ADT plus antiandrogen) as compared with ADT alone (Klotz 2001).

Despite ADT, virtually all patients with recurrent disease will progress and their disease will spread to distant sites, most commonly bones and/or regional lymph nodes (Scher 1996, Small 1997). Disseminated or metastatic castrate-resistant prostate cancer (mCRPC) is a noncurable and lethal disease with a median survival reported in recent Phase 3 studies ranging from 12.2 to 27.2 months (Kantoff 2010, Ryan 2013).

Until recently, docetaxel was the only therapy demonstrated to enhance overall survival in patients with mCRPC (Petrylak 2004, Tannock 2004). However, since 2010, sipuleucel-T (Provenge®, Provenge 2012), cabazitaxel (Jevtana®, Jevtana 2012), abiraterone acetate (Zytiga®, Zytiga 2012), and enzalutamide (Xtandi®, Xtandi 2011) have all received Food and Drug Administration (FDA) approval for the treatment of mCRPC based on their demonstrated ability to increase overall survival. This increasing repertoire of approved agents for the treatment of mCRPC creates challenges within the treatment paradigm as there are currently no clinical data to inform how these agents are best sequenced.

Although enzalutamide is indicated for the treatment of patients with mCRPC who have received prior chemotherapy, it has also been listed in the National Comprehensive Cancer Network Guidelines for prechemotherapy treatment of patients with mCRPC who have an evidence level 2A. Sipuleucel-T and enzalutamide both have the potential to be administered prior to chemotherapy to asymptomatic or minimally symptomatic patients with mCRPC. Because androgen ablation has been demonstrated to have immunostimulatory properties, there is potential synergy from combining the androgen receptor inhibitor enzalutamide with sipuleucel-T (Mercader 2001, Drake 2005, Gannon 2009, Sutherland 2005, Koh 2009, Madan 2008). An evidence-based approach to assess the consequences of concurrent or sequential therapy with enzalutamide and sipuleucel-T is therefore warranted to optimize the benefits of these agents within the therapeutic paradigm.

1.1.2 Sipuleucel-T

Sipuleucel-T is an autologous cellular immunotherapy product designed to stimulate an immune response against prostate cancer. It consists of autologous peripheral blood mononuclear cells (PBMCs), including antigen presenting cells (APCs, defined as large CD54-positive PBMCs) that have been activated in vitro with prostate antigen PA2024, a recombinant fusion protein composed of prostatic acid phosphatase (PAP) linked to granulocyte-macrophage colony-stimulating factor (GM-CSF).

Sipuleucel-T was approved in the United States in 2010 for the treatment of men with asymptomatic or minimally symptomatic (hormone refractory) mCRPC (Provenge 2011). In the pivotal trial D9902B (IMPACT), 512 patients were randomized 2:1 to receive sipuleucel-T (N=341 subjects) or control (N=171 subjects). Overall survival was longer in the sipuleucel-T group (median of 25.8 months versus 21.7 months; hazard ratio [HR] = 0.78; 95% confidence interval [CI]: 0.62, 0.98; P=0.03). More than 3,339 infusions of sipuleucel-T and control (a product manufactured from PBMCs without activation with the PA2024 antigen), have been administered to men with prostate cancer in clinical trials.

Clinical data to support the safety of sipuleucel-T are provided from 904 subjects (sipuleucel-T, N = 601; control, N = 303) who participated in 4 multicenter, randomized, double-blind, controlled Phase 3 studies (Provenge 2011). Three of these studies were conducted in men with mCRPC (studies D9902B, D9901, and D9902A), and 1 study was conducted in men with androgen dependent prostate cancer (ADPC). In the 4 randomized Phase 3 studies, adverse events (AEs) reported in ≥ 20% of all subjects were chills, fatigue, pyrexia, and back pain. The most common AEs (observed in ≥ 5% of sipuleucel-T subjects as well as at least twice the rate of that in control subjects) included chills, pyrexia, headache, myalgia, influenza-like illness, and hyperhidrosis. The majority of these events occurred within 1 day of infusion; were grade 1 or 2 in severity; and were generally of short duration (i.e., resolved in ≤ 2 days). Grade 3 or 4 events were reported in 27.6% of subjects in the sipuleucel-T group, compared with 28.4% in the control group. Cerebrovascular events (CVEs) occurred in 3.5% of subjects in the sipuleucel-T group compared with 2.6% in the control group. A registry of approximately 1,500 patients is ongoing and will further evaluate the risk of CVEs in subjects receiving sipuleucel-T.

1.1.3 Enzalutamide

Enzalutamide was approved in the U.S. in August, 2012 for the treatment of men with mCRPC who have previously received docetaxel (Xtandi 2012). Enzalutamide is an androgen receptor inhibitor that acts on several steps in the androgen receptor signaling pathway.

In the pivotal AFFIRM trial, 1199 patients were randomized 2:1 to receive oral enzalutamide (160 mg per day, N=800 subjects) or placebo (N=399 subjects). Overall survival was longer in the enzalutamide group (median of 18.4 months versus 13.6 months; HR=0.63; 95% CI: 0.53, 0.75, P < 0.001) (Scher 2008). Common AEs associated with enzalutamide included some National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, NCI 2010) grade 3-4 events that had a ≥ 2% absolute increase in frequency in the enzalutamide arm compared to the placebo arm. These included asthenic conditions, peripheral edema, back pain, arthralgia, musculoskeletal pain, muscular weakness, musculoskeletal weakness, diarrhea, hot flush, hypertension, headache, dizziness, spinal cord compression and cauda equina syndrome, paresthesia, mental impairment disorders, hypoesthesia, upper respiratory tract infections, lower respiratory tract and lung infection, insomnia, anxiety, hematuria, pollakiuria, fall, nonpathologic fractures, pruritus, dry skin, and epistaxis. Seven out of 800 enzalutamide-treated subjects (0.9%) experienced a seizure and were discontinued from the study. Grade 3 and 4 AEs were reported among 47% of enzalutamide-treated subjects and 53% of placebo-treated subjects (Xtandi 2012).

Medivation, Inc., the manufacturer of enzalutamide, is conducting a Phase 3 study of enzalutamide vs. placebo in patients with mCRPC who have not undergone chemotherapy for prostate cancer. The randomized, double-blind, placebo-controlled PREVAIL Trial is scheduled

to enroll 1680 patients to determine the benefit of enzalutamide versus placebo as assessed by overall survival and progression free survival in this population.

2.0 OBJECTIVES

2.1 Primary Objective

To evaluate peripheral PA2024-specific T cell immune response to sipuleucel-T over time via a T cell stimulation index from a proliferation assay.

2.2 Secondary Objectives

Secondary Objectives:

- To evaluate time to PSA progression.
- To estimate the percent of subjects who are PSA progression-free at 12 months.
- To evaluate overall survival.
- To determine the magnitude of peripheral immune response over time as determined by the following:
  - Peripheral PAP-specific T cell immune response to sipuleucel-T over time via T cell stimulation index from a proliferation assay.
  - T cell interferon-γ enzyme-linked immunosorbent spot assay (ELISPOT) response to PA2024 and PAP.
  - Humoral response to PA2024 and PAP by enzyme-linked immunosorbent assay (ELISA).
  - Chemokine and cytokine production via fluorescent immunoassay (Luminex® assay).
- To evaluate safety.

2.3 Exploratory Objectives

- To evaluate time to next anticancer intervention.
- To evaluate time to first cancer-related opioid use (see Section 6.5).

- To evaluate time to Eastern Cooperative Oncology Group (ECOG) performance status decline.

3.0 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is a randomized, open-label study designed to assess the effects of sipuleucel-T when administered concurrently or sequentially with enzalutamide. This study consists of 3 phases. The screening phase will begin at the completion of the informed consent process and continue through registration. The active phase will begin at registration and continue through the post-treatment visit (30 to 37 days following the last study treatment). The long-term follow-up (LTFU) phase will begin after the post-treatment visit and will continue until the subject's death or until Dendreon terminates the study.

Eligible subjects will be registered and randomly assigned in a 1:1 ratio to receive 3 infusions of sipuleucel-T in addition to a total of 52 weeks of concurrent or sequential treatment with enzalutamide. Subjects will be stratified by screening PSA levels (≥ 25 ng/mL, yes or no) and screening lactate dehydrogenase (LDH) levels (≥ 200 IU/L, yes or no), both obtained from the central laboratory.

Enzalutamide treatment will occur either concurrently with sipuleucel-T (concurrent arm), or following administration of sipuleucel-T (sequential arm):

Concurrent Arm

Subjects will receive sipuleucel-T concurrently with enzalutamide (160 mg orally once daily). Enzalutamide treatment will start 2 weeks prior to the first leukapheresis and continue for 52 weeks or until disease progression or unacceptable toxicity, whichever occurs first. Subjects randomized to the concurrent arm who receive the 2-week enzalutamide run-in, but do not subsequently receive at least one partial (> 0 mL) infusion of sipuleucel-T will not receive any additional enzalutamide treatment, will undergo a post-treatment visit, and will enter the LTFU phase.

Sequential Arm

Subjects will receive sipuleucel-T followed by enzalutamide (160 mg orally once daily). Enzalutamide treatment will start approximately 10 weeks after the first infusion of sipuleucel-T and continue for 52 weeks or until disease progression or unacceptable toxicity, whichever occurs first. Subjects randomized to the sequential arm who do not receive at least one partial (> 0 mL) infusion of sipuleucel-T will not receive any enzalutamide treatment, will undergo a post-treatment visit, and will enter the LTFU phase.

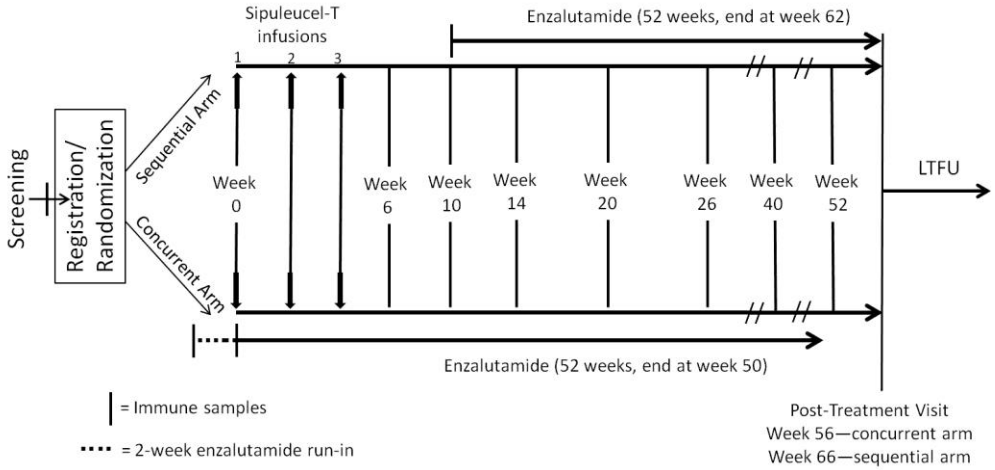
After 52 weeks of enzalutamide treatment provided by Dendreon, subjects in either treatment arm may continue to receive enzalutamide obtained from other sources at the discretion of their treating physician. Dendreon cannot provide enzalutamide beyond the protocol-specified duration of 52 weeks.

During the active phase, subjects in both arms will undergo a standard 1.5 to 2.0 blood volume leukapheresis, followed approximately 3 days later by an intravenous (IV) infusion of sipuleucel-T. This process will occur a total of 3 times at approximately 2-week intervals. A course of sipuleucel-T treatment comprises 3 infusions. Immune monitoring blood samples will be drawn and clinical and safety assessments will be performed at screening, preleukapheresis visits 2 and 3, and weeks 6, 10, 14, 20, 26, 40, and 52, with the timing of visits based on the date of the first sipuleucel-T infusion. Immune monitoring blood samples will also be drawn following each sipuleucel-T infusion. Additional assessments including physical examinations, vital signs, ECOG performance status (see Appendix 1), AE monitoring, anticancer therapies, first opioid use for cancer-related pain, laboratory tests (e.g., hematology and serum chemistries), and PSA monitoring will be performed at the times shown in Table 1.

During the LTFU phase, safety (treatment-related AEs, seizures, and CVEs), survival status, PSA, ECOG performance status, first opioid use for cancer-related pain (if applicable), and anticancer therapies will be assessed every 3 months until the subject's death or until Dendreon terminates the study.

The study design is illustrated in Figure 1.

Figure 1: Study Schematic



Abbreviation: LTFU = long-term follow-up.

4.0 STUDY POPULATION

To participate in this study, subjects must meet all inclusion criteria and none of the exclusion criteria.

4.1 Inclusion Criteria

4.1.1 Written informed consent provided prior to the initiation of study procedures.

4.1.2 Age ≥ 18 years.

4.1.3 Histologically documented adenocarcinoma prostate cancer confirmed by a pathology report from prostate biopsy or a radical prostatectomy specimen. If prostatic tumor is of mixed histology, > 50% of the tumor must be adenocarcinoma.

4.1.4 Metastatic disease as evidenced by one of the following:

- Bone metastasis (≥ 1 lesion) by bone scan or by sodium-fluoride positron emission tomography (Na-F PET) or carbon-11 acetate positron emission tomography (C11 acetate PET) with computed tomography (CT). If a bone scan is used, solitary lesions or lesions which could be attributed to causes other than metastatic prostate cancer must be confirmed with a second imaging modality (i.e., CT or magnetic resonance imaging [MRI]).

- Lymph node metastasis comprising at least 1 node ≥ 2 cm in short-axis diameter.

Histopathological confirmation of metastatic disease is not required.

4.1.5 Castrate-resistant prostate cancer, in the setting of castrate levels of testosterone (≤ 50 ng/dL), defined as current or historical evidence of disease progression concomitant with surgical castration or ADT, as demonstrated by one of the following:

- Prostate specific antigen progression: PSA progression will be defined as 2 rising PSA values compared to a reference value, measured at least 7 days apart and the second value is ≥ 2 ng/mL (Scher 2008).

- Progression of measurable disease: ≥ 20% increase in the sum of the longest diameters of all measureable lesions or the development of any new lesions. The change will be measurable against the best response to castration therapy or against the precastration measurements if there was no response.

- Progression of non-measurable disease by one of the following:

  – 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 precastration studies if there was no response.

  – Bone disease:

    - Bone scan: 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 precastration studies if there was no response. Increased uptake of pre-existing lesions on bone scan does not constitute progression.

    - Na-F or C-11 acetate PET/CT: Appearance of 2 or more new lesions when compared to imaging acquired during castration therapy or against the precastration studies if there was no response.

4.1.6 Castration levels of testosterone (≤ 50 ng/dL) achieved via medical or surgical castration.

4.1.7 Serum PSA ≥ 2.0 ng/mL.

4.1.8 Screening ECOG performance status ≤ 1 (see Appendix 1).

4.1.9 Adequate screening hematologic, renal, and liver function as evidenced by laboratory test results obtained from the central laboratory within the following ranges ≤ 28 days prior to registration:

• Absolute lymphocyte count	≥ 1 x 10^3/μL
• White blood cell count	≥ 2.5 x 10^3/μL
• Neutrophils	≥ 1 x 10^3/μL
• Platelet count	≥ 100 x 10^3/μL
• Hemoglobin	≥ 10.0 g/dL
• Creatinine	≤ 2.0 mg/dL
• Total bilirubin	≤ 2 x upper limit of normal (ULN)
• Aspartate aminotransferase	≤ 2.5 x ULN
• Alanine aminotransferase	≤ 2.5 x ULN

4.1.10 Negative serology test for human immunodeficiency virus 1 and 2.

4.1.11 Resides within driving distance (round trip within 1 day) of the clinical trial site for the duration of the active phase.

4.2 Exclusion Criteria

4.2.1 The presence of known lung, liver, or brain metastases, malignant pleural effusions, or malignant ascites. In the case of suspected or questionable findings, the investigator must assess and document each finding in the subject's medical record prior to registration.

4.2.2 Spinal cord compression, imminent long bone fracture, or any other condition that, in the opinion of the investigator, is likely to require radiation therapy and/or steroids for pain control during the active phase.

4.2.3 History of stage 3 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 1 or 2 cancer must have been adequately treated and been disease free for ≥ 3 years at the time of registration.

4.2.4 History of seizures or of predisposing factors for seizures, including underlying brain injury with loss of consciousness within previous 12 months, transient ischemic attack within previous 12 months, cerebral vascular accident or brain arteriovenous malformation.

4.2.5 Child-Pugh Class C hepatic insufficiency (see Appendix 2).

4.2.6 History of allergic reactions attributed to compounds of similar chemical or biologic composition to sipuleucel-T, GM-CSF or granulocyte colony stimulating factor (G-CSF).

4.2.7 Previous treatment with sipuleucel-T or enrollment in a sipuleucel-T trial, regardless of whether the subject received sipuleucel-T or control.

4.2.8 Previous treatment with enzalutamide.

4.2.9 Previous treatment with abiraterone acetate.

4.2.10 Previous treatment with ipilimumab.

4.2.11 Previous treatment with ketoconazole other than topical use or for treatment of infections (e.g., oral thrush); most recent use must have been ≥ 7 days prior to registration.

4.2.12 Previous treatment with any immunotherapy or investigational vaccine.

4.2.13 A requirement for ongoing systemic immunosuppressive therapy. Use of inhaled, intranasal, intra-articular, and topical steroids is allowed. Oral or IV steroids to prevent or treat IV contrast reactions are allowed.

4.2.14 Previous treatment with chemotherapy for mCRPC, or chemotherapy for any reason ≤ 2 years prior to registration.

4.2.15 Use of concomitant medications that may lower the seizure threshold or the use of antiseizure medications ≤ 1 year prior to registration.

4.2.16 Received GM-CSF or G-CSF ≤ 90 days prior to registration.

4.2.17 Ongoing non-steroidal antiandrogen withdrawal response. Subjects on combined androgen blockade with a non-steroidal antiandrogen and LHRH agonist must discontinue the non-steroidal antiandrogen. A PSA level must be obtained < 28 days prior to the antiandrogen discontinuation and then again > 28 days following discontinuation. If the PSA has dropped > 25% from the time of antiandrogen discontinuation, subjects are not eligible until the PSA rises above the post-antiandrogen discontinuation nadir.

4.2.18 Any of the following medications or interventions ≤ 28 days prior to registration:

- Radiation therapy, either via external beam or brachytherapy.
- Any systemic steroid. Use of inhaled, intra-nasal, intra-articular, and topical steroids is allowed. Oral or IV steroids to prevent or treat IV contrast reactions are allowed.

- Any systemic therapy for prostate cancer, except for ADT.
- Any investigational product for prostate cancer.
- Major surgery requiring general anesthesia, with the exception of placement of central venous catheters.
- Inducers and inhibitors of cytochrome P450 (CYP) enzyme CYP2C8 (gemfibrozil and rifampin [see Appendix 3]).
- Medications that are metabolized by CYP3A4, CYP2C9, or CYP2C19 that have a narrow therapeutic index (see Appendix 3).
- Inducers of CYP3A4 (including but not limited to phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, and phenobarbital [see Appendix 3]).

4.2.19 A requirement for treatment with opioid analgesics for cancer-related pain ≤ 21 days prior to registration.

4.2.20 An active infection requiring parenteral antibiotic therapy or causing fever (temperature > 100.5˚ F or 38.1˚ C) ≤ 1 week prior to registration.

4.2.21 Any medical intervention, any other condition, or any other circumstance which, in the opinion of the investigator or the Dendreon medical monitor, could compromise adherence with study requirements or otherwise compromise the study's objectives.

4.3 Discontinuation from Study Treatments or Assessments

The investigator may withdraw a subject from one or both study treatments, or from study assessment, if, in his or her clinical judgment, it is in the best interest of the subject.

4.3.1 Discontinuation from Sipuleucel-T Treatment

Subjects who have received at least 1 partial (> 0 mL) infusion of sipuleucel-T may discontinue sipuleucel-T without the requirement to discontinue enzalutamide, provided the criteria for removal from all study treatments (see Section 4.3.3) have not been met. These subjects will continue all protocol-specified assessments in the active phase.

Any toxicity requiring sipuleucel-T discontinuation will be recorded as an AE in the subject's medical record and on the case report form (CRF).

4.3.2 Discontinuation from Enzalutamide Treatment

Dose reduction for enzalutamide will not be permitted and subjects with any toxicity requiring enzalutamide dose reduction must discontinue enzalutamide treatment.

Subjects who have not received 3 sipuleucel-T infusions may discontinue enzalutamide treatment without the requirement to discontinue sipuleucel-T provided the criteria for removal from all study treatments (Section 4.3.3) have not been met. These subjects will undergo a post-treatment visit after the last sipuleucel-T infusion and enter the LTFU phase.

Subjects who have already received 3 sipuleucel-T infusions and ≥ 10 weeks of enzalutamide treatment when they discontinue enzalutamide will continue all protocol-specified assessments in the active phase. Subjects who have received less than 10 weeks of enzalutamide treatment when they discontinue enzalutamide will undergo a post-treatment visit and enter the LTFU phase.

Any toxicity requiring enzalutamide discontinuation or dose reduction will be recorded as an AE in the subject's medical record and on the CRF.

4.3.3 Discontinuation from All Study Treatments

Subjects will discontinue from all study treatments, undergo a post-treatment visit, and enter the LTFU phase for any of the following reasons:

- The subject withdraws consent to receive study treatments.
- The subject is unable to, or refuses to, undergo leukapheresis.
- The subject is unable to, or refuses to, receive at least 1 partial (> 0 mL) sipuleucel-T infusion.
- Dendreon is unable to manufacture sipuleucel-T for the subject.
- The subject develops disease progression as defined in Section 4.5.
- The subject develops any condition requiring a prohibited treatment (see Section 4.7).
- Treatment is stopped at the discretion of the investigator or Dendreon.

4.3.4 Discontinuation from the Study

Subjects may discontinue their participation in the trial at any time without prejudice. If a subject withdraws consent for any further study involvement, complete withdrawal of consent must be documented in the subject's medical record. The date and reason for withdrawal will be recorded in the subject's medical record and on the CRF.

Whenever possible, subjects discontinuing from the study will undergo a post-treatment visit. All AEs considered by the investigator to be related to study treatment(s) that are ongoing at the time of discontinuation will be followed by the investigator until resolution or until the subject returns to baseline. The investigator should make every reasonable attempt to ensure that the subject is contacted (via telephone or during a post-treatment visit) to obtain the final status of any AEs and concomitant medications.

Subjects will discontinue from the study (all treatment and subsequent assessments) for any of the following reasons:

- The subject withdraws consent for any reason.
- The subject loses the ability to freely provide consent.
- The subject is lost to follow-up.
- The subject fails to comply with protocol requirements.
- The subject is discontinued from the study at the discretion of the investigator or Dendreon.
- Dendreon terminates the study.

Subjects who withdraw consent, or lose the ability to freely provide consent, will be followed by the investigator for survival every 3 months using the Social Security Death Index (SSDI) and National Death Index (NDI). Date of death, where available, will be recorded in the subject's medical record and on the CRF.

4.4 Lost to Follow-Up

If the subject fails to respond to requests for follow-up, the clinical trial site will send a registered letter, at a minimum, to the subject requesting contact with the clinic. All attempts to resume contact (including copies of written correspondence) will be included in the source documentation. Subjects who do not respond to requests for follow-up after all reasonable attempts to establish contact will be considered "lost to follow-up". Subjects who are lost to

follow-up will be followed by the investigator for survival every 3 months using the SSDI and the NDI. Date of death, where available, will be recorded in the subject's medical record and on the CRF.

4.5 Disease Progression

Disease progression is determined by the investigator per the definition below. The earliest date of disease progression will be recorded in the subject's medical record and on the CRF. Following disease progression, all study treatments will cease, the subject will undergo a post-treatment visit, enter LTFU, and will be treated at the investigator's discretion.

Any 1 or more of the following events constitutes disease progression:

- PSA Progression (based on Prostate Cancer Working Group 2 criteria, (Scher 2008):
  - Decline from baseline: the first PSA increase that is ≥ 25% and ≥ 2 ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later (i.e., a confirmed rising trend).
  - No decline from baseline: PSA progression ≥ 25% and ≥ 2 ng/mL after 12 weeks of enzalutamide treatment.

PSA measurements obtained during the first 12 weeks of enzalutamide treatment should not be used as the sole criterion for determining progression. Study treatments may be continued in equivocal cases where there is PSA progression but no clear evidence of disease progression or clinical deterioration, and where the investigator feels the subject is deriving clinical benefit from the study treatments and subject safety is not compromised (Scher 2008).

- Clinically significant disease-specific event:
  - New spinal cord or nerve root compression.
  - New pathologic fracture.
  - Development of metastatic disease in a new anatomic location.
  - Disease progression based on radiographic imaging and Response Evaluation Criteria in Solid Tumors criteria version 1.1.

4.6 Concomitant Medications

Subjects should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, or other therapies, in accordance with standard practice at the clinical trial site. Subjects receiving ADT, bisphosphonate therapy such as zoledronic acid (Zometa®), or denosumab (Xgeva®) at the time of registration should continue the therapy at a stable dose until the post-treatment visit or disease progression, whichever occurs first.

All concomitant medications administered from screening through the post-treatment visit, including indication, dose, route, frequency and treatment dates, will be recorded in the subject's medical record and on the CRF. After the post-treatment visit, only anticancer therapies will be recorded. The first opioid taken for cancer-related pain will be recorded, regardless of when it is started.

4.7 Prohibited and/or Restricted Treatments

Subjects on ADT must continue this therapy until the post-treatment visit or disease progression, whichever occurs first.

The following medications and interventions must not be initiated until the post-treatment visit or disease progression, whichever occurs first:

- Investigational vaccines or other investigational products.
- Ipilimumab.
- Any therapy for prostate cancer except for that administered in this protocol and ADT.
- External beam radiation therapy or brachytherapy.
- Inducers or inhibitors of CYP2C8 (gemfibrozil, rifampin [see Appendix 3]).
- Medications that are metabolized by CYP3A4, CYP2C9, or CYP2C19 that have a narrow therapeutic index (see Appendix 3).
- Inducers of CYP3A4 (including but not limited to phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, and phenobarbital [see Appendix 3]).

5.0 STUDY TREATMENTS

5.1 Handling Study Treatments

Study treatments must be stored, handled, and prepared as specified by the sipuleucel-T investigator's brochure (IB, Sipuleucel-T 2013) and the enzalutamide prescribing information (Xtandi 2012). Dendreon should be notified immediately if concerns regarding the quality or appearance of the study treatments arise.

Accountability documentation, including receipt, storage and applicable storage conditions, administration, destruction and use of required processes must be maintained to ensure the study treatments are accurately administered.

Dendreon will supply the study treatments (sipuleucel-T, enzalutamide). Enzalutamide will be labeled with protocol-specific information, including the statement "Caution: New Drug-Limited by United States law to investigational use."

5.2 Sipuleucel-T Treatment

5.2.1 Leukapheresis and Infusion Scheduling

The subject's 3 leukapheresis appointments will be scheduled by Dendreon. Leukapheresis appointments will be scheduled at approximately 2-week intervals. The clinical trial site will receive confirmation of the leukapheresis and infusion dates via email. The clinical trial site will schedule the subject's infusion appointments based on this schedule. If the subject is subsequently deemed ineligible, the clinical trial site will be informed and the leukapheresis and infusion appointments will be canceled.

5.2.2 Preleukapheresis Assessments

Subjects will be evaluated for their ability to tolerate the leukapheresis procedure during preleukapheresis assessments that occur during screening and ≤ 5 days prior to the second and third leukapheresis. The assessment may occur on the day of the leukapheresis procedure provided it occurs before the leukapheresis procedure.

Venous access is evaluated to determine if, due to inadequate peripheral veins, placement of a central venous catheter is absolutely necessary to undergo leukapheresis. If there is any question about adequate venous access, the subject will be assessed at a leukapheresis center by a leukapheresis nurse.

If a subject has any infection requiring parenteral antibiotic therapy or causing fever (temperature > 100.5°F or > 38.1°C) within 1 week prior to a leukapheresis appointment, the

appointment should be rescheduled to occur after the fever resolves and the investigator believes the subject is healthy enough to undergo the procedure.

5.2.3 Subject Preparation for Leukapheresis

The subject should be instructed to eat calcium-rich foods in advance of the leukapheresis procedure. The subject should drink plenty of fluids a few days prior to the procedure to promote adequate venous access during leukapheresis, but drink minimal fluids on the mornings of leukapheresis appointments.

5.2.4 Leukapheresis

The collection of blood cells to manufacture sipuleucel-T is analogous to that for autologous blood transfusions. Subjects undergo a standard 1.5 to 2.0 blood volume leukapheresis to harvest PBMCs (primarily lymphocytes and monocytes). Prior mobilization with a colony-stimulating factor is not performed. Immediately after completion of the collection procedure, the leukapheresis product is transported to one of Dendreon's regional immunotherapy manufacturing facilities. All of the cells recovered from the leukapheresis procedure will be used to produce 1 dose of sipuleucel-T that is infused approximately 3 days following the leukapheresis procedure.

To maintain the chain of identity and ensure subject safety, subject identifiers accompany the production of sipuleucel-T throughout the manufacturing process. The subject's identifying information will be revealed to Dendreon's apheresis and manufacturing personnel. The sipuleucel-T label with the subject identifier is returned to the clinical trial site.

5.2.5 Sipuleucel-T Infusion

Each sipuleucel-T dose is released by Dendreon for infusion approximately 3 days following the leukapheresis procedure. Subjects will be infused according to the infusion guidelines provided in Appendix 4.

5.2.6 Sipuleucel-T Product Failures and Leukapheresis Rescheduling

In the event that a subject's leukapheresis procedure fails, sipuleucel-T does not meet quality release specifications, or infusion is not possible for any other reason, the subject may be scheduled to undergo a repeat leukapheresis procedure. A minimum of 2 days must have elapsed since the last leukapheresis procedure. Scheduling will depend upon capacity of the leukapheresis and Dendreon manufacturing facilities. If the second or third leukapheresis appointment is delayed or rescheduled for any reason, a physical examination and all other

preleukapheresis procedures must be repeated within the 5 days prior to the next leukapheresis procedure. The preleukapheresis immune monitoring samples will not be drawn again.

There is a possibility that a subject's sipuleucel-T may fail to meet quality requirements more than once. In such instances, the subject may not receive all 3 infusions. In rare instances, it may be determined that it is not possible to manufacture sipuleucel-T that passes quality control (QC) testing from a subject's leukapheresis product.

5.3 Enzalutamide Treatment

For the concurrent arm, enzalutamide dispensing visits will occur 2 weeks prior to the first leukapheresis, at preleukapheresis visit 2 and at weeks 6, 10, 14, 20, 26, 34, 40, and 46; for the sequential arm, these visits will occur at weeks 10, 14, 20, 26, 34, 40, 48 and 52 (see Table 1).

In the event of multiple sipuleucel-T product failures for a subject in the sequential arm, enzalutamide treatment should not be started until the subject has received all 3 sipuleucel-T infusions or a determination has been made that the subject will not receive 3 infusions. Subjects randomized to the sequential arm who do not receive at least one partial (> 0 mL) infusion of sipuleucel-T will not receive any enzalutamide treatment.

5.4 Selection and Timing of Dose for Each Subject

Subjects who complete the study will receive 3 infusions of sipuleucel-T and 52 weeks of enzalutamide (160 mg oral dose once daily). The timing of doses is described in Section 3.1.

5.5 Blinding/Unblinding

This is an open-label study.

5.6 Treatment Compliance

Sipuleucel-T will be administered at the clinical trial site.

Enzalutamide compliance will be monitored by reconciliation of returned study treatments and/or treatment packaging at every dispensing visit.

5.7 Destruction and Return of Study Treatments

5.7.1 Sipuleucel-T

The clinical trial site will dispose of the sipuleucel-T bag and tubing according to institutional procedures for disposal of biohazardous waste that contains human blood.

All packaging materials and gel packs will be disposed of according to institutional procedures.

If instructed by Dendreon to return the sipuleucel-T and/or tubing, the remaining sipuleucel-T will be placed in the original shipping box with the original packaging materials and shipped per Dendreon's instructions.

5.7.2 Enzalutamide

All undispensed, returned, or expired enzalutamide and any empty enzalutamide bottles will be retained until study treatment accountability and treatment compliance are verified by a Dendreon clinical research associate. Following verification, any undispensed, returned or expired enzalutamide and any empty enzalutamide bottles will be disposed of according to institutional procedures.

6.0 STUDY ASSESSMENTS AND PROCEDURES

6.1 Schedule of Assessments

The schedule of assessments is presented in Table 1.

Table 1: Schedule of Assessments

		Active Phase						LTFU Visits[f]
	Screening	**Enzalutamide Dispensing Visits[a]**	**Preleukapheresis Visits[b]**	**Leukapheresis Visits[c]**	**Infusion Visits[d]**	**Post-infusion Visits[e]**	**Post-Treatment Visit**	
Visit Timing	**≤ 28 days prior to registration[g]**	**± 1 week**	**≤ 5 days prior to leukapheresis**	**As scheduled by Dendreon**	**Approximately 3 days after leukapheresis**	**± 1 week**	**30-37 days after last study treatment**	**± 2 weeks**
Informed Consent	X							
Registration/ Randomization	X							
Pathology (Gleason Sum)	X							
Leukapheresis				X				
Sipuleucel-T Infusion					X			
Enzalutamide Dispensing		X						
Clinical Assessments								
Medical History	X							
Physical Examination	X		X			X	X	
Vital Signs	X		X		X[h]	X	X	
ECOG Performance Status	X		X			X	X	X[i]
Bone scan or Na-F or C11 acetate PET/CT; cross-sectional imaging (CT or MRI)	X							

Table 1: Schedule of Assessments (Cont'd)

		Active Phase						
	Screening	**Enzalutamide Dispensing Visits[a]**	**Preleukapheresis Visits[b]**	**Leukapheresis Visits[c]**	**Infusion Visits[d]**	**Post-infusion Visits[e]**	**Post-Treatment Visit**	**LTFU Visits[f]**
Visit Timing	**≤ 28 days prior to registration[g]**	**± 1 week**	**≤ 5 days prior to leukapheresis**	**As scheduled by Dendreon**	**Approximately 3 days after leukapheresis**	**± 1 week**	**30-37 days after last study treatment**	**± 2 weeks**
Safety Assessments								
Record Adverse Events		X	X	X	X	X	X	X[j]
Record Serious Adverse Events		X	X	X	X	X	X	X[j]
Record Cerebrovascular Events		X	X	X	X	X	X	X
Record Seizures		X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X[k]
Anticancer Therapies	X	X	X	X	X	X	X	X
First Opioid for Cancer-related Pain		X	X	X	X	X	X	X
Survival Status								X
Laboratory Assessments								
Hematology	X		X			X	X	
Chemistry	X		X			X	X	
Testosterone	X							
PSA	X	X[l]			X[l]	X	X	X[m]
Serum PAP	X	X[l]			X[l]	X	X	

Table 1: Schedule of Assessments (Cont'd)

		Active Phase						LTFU Visits[f]
	Screening	**Enzalutamide Dispensing Visits[a]**	**Preleukapheresis Visits[b]**	**Leukapheresis Visits[c]**	**Infusion Visits[d]**	**Post-infusion Visits[e]**	**Post-Treatment Visit**	
Visit Timing	**≤ 28 days prior to registration[g]**	**± 1 week**	**≤ 5 days prior to leukapheresis**	**As scheduled by Dendreon**	**Approximately 3 days after leukapheresis**	**± 1 week**	**30-37 days after last study treatment**	**± 2 weeks**
Coagulation	X							
Serology	X							
Immune Monitoring Assessments								
100 mL sample	X[n]		X[o]			X	X	
10 mL sample					X[p]			

Abbreviations: CT = computed tomography; DNA = deoxyribonucleic acid; ECOG = Eastern Cooperative Oncology Group; LFTU = long-term follow-up; MRI = magnetic resonance imaging; Na-F = sodium fluoride; PAP = prostatic acid phosphatase; PET = positron emission tomography; PSA = prostate specific antigen.

a For the concurrent arm, enzalutamide dispensing visits will occur 2 weeks prior to the first leukapheresis, at the preleukapheresis 2 visit, and at weeks 6, 10, 14, 20, 26, 34, 40 and 46; for the sequential arm, these visits will occur at weeks 10, 14, 20, 26, 34, 40, 48 and 52.

b Applies to leukapheresis visits 2 and 3 only; preleukapheresis visits will occur ≤ 5 days prior to each leukapheresis.

c In the concurrent arm, the first leukapheresis should occur 2 weeks after the start of enzalutamide and must occur within 42 days of the start of enzalutamide.

d Infusions will occur approximately 3 days after leukapheresis at approximately 2-week intervals.

e Post-infusion visits will occur at weeks 6, 10, 14, 20, 26, 40, and 52.

f Long term follow-up visits will occur every 3 months until the subject's death or until Dendreon terminates the study. The first LTFU visit will occur 3 months after the post-treatment visit.

g All screening procedures must occur within 28 calendar days prior to registration, with the exception of written informed consent, histological documentation of prostate cancer with Gleason grading, and imaging for confirmation of metastatic disease.

h Vital signs will be measured 1 to 30 minutes prior to, and at 30 minutes (± 10 min) following each infusion.

i ECOG performance status will be collected during LTFU as long as the subject continues to receive enzalutamide. Once the subject discontinues enzalutamide, a final ECOG performance status will be collected at the next LTFU visit and subsequent visits will be conducted via telephone.

j Only treatment-related events will be collected.

k Only medications taken for treatment-related adverse events will be collected.

l Serum PAP and PSA will be collected at the first enzalutamide dispensing visit and at the first and third sipuleucel-T infusions.
m Serum PSA will be collected during LTFU as long as the subject continues to receive enzalutamide. Once the subject discontinues enzalutamide, a final serum PSA will be collected at the next LTFU visit and subsequent visits will be conducted via telephone.
n Baseline DNA analysis sample is collected at screening only.
o Immune monitoring blood samples (100 mL) will be collected from all subjects who receive at least 1 partial infusion (> 0 mL). If the subject receives only 1 or 2 infusions, immune monitoring samples will still be drawn at subsequent preleukapheresis visit time points.
p A 10-mL blood sample will be collected 3 hours (allowable window 1-24 hours) after completion of the infusion.

6.1.1 Registration

The clinical trial site will preregister every subject who provides written informed consent and a unique subject number will be assigned by Dendreon. Registration documents will be completed and submitted to Dendreon for all subjects who meet all eligibility criteria.

Subjects who do not meet all eligibility criteria will be considered screen failures and no further procedures will be conducted. The reason(s) for each screen failure will be recorded in the subject's medical record and on the CRF.

6.1.2 Randomization

Eligible subjects will be registered and randomly assigned in a 1:1 ratio to receive 3 infusions of sipuleucel-T in addition to a total of 52 weeks of therapy with enzalutamide either concurrently with sipuleucel-T (concurrent arm), or following administration of sipuleucel-T (sequential arm). Subjects will be stratified by PSA levels (≥ 25 ng/mL, yes or no) obtained from the central laboratory and LDH levels (≥ 200 IU/L, yes or no) obtained from the central laboratory. Subjects will generally be randomized on the same day as registration.

6.2 Demographics

Demographic information, including birth date, race and ethnicity will be recorded in the subject's medical record and on the CRF.

6.3 Clinical Assessments

Clinical assessments will be performed at the times noted in Table 1.

6.3.1 Medical History

Significant historic and current medical conditions or illness, allergies to medications, and prior surgical interventions will be recorded in the subject's medical record and on the CRF. Information regarding the subject's history of smoking and other risk factors for CVEs will also be recorded.

Symptoms that are ongoing at the time of, or that develop after the subject provides informed consent and before registration, will also be considered medical history.

Medical history will include the subject's 6 most recent PSA values, vaccinations in the two years prior to registration, and all prior anticancer therapies.

6.3.2 Physical Examination

Physical examinations will be performed at the times noted in Table 1 and must be conducted by an appropriately qualified investigator listed on the Form FDA 1572.

The physical examinations conducted at screening and at preleukapheresis visits will include a review of the skin, pulmonary, cardiovascular, and neurologic systems, abdomen, and extremities. A review of additional body systems will be at the discretion of the investigator.

For all other visits that call for a physical examination, the body systems reviewed will be at the discretion of the investigator.

Each physical examination will include weight measurement. Height will be measured at screening only.

Abnormal physical examination findings at screening will be considered part of the medical history and will be recorded on the Medical History CRF. Any new or worsening physical examination findings identified after the subject's registration will be considered AEs and will be recorded in the subject's medical record and on the CRF.

6.3.3 Vital Signs

Vital signs (respiration rate, temperature, heart rate, and blood pressure) will be measured at the times noted in Table 1. Vital signs will be recorded in the subject's medical record and on the CRF .

6.3.4 ECOG Performance Status

Eastern Cooperative Oncology Group performance status (see Appendix 1) will be assessed at the times noted in Table 1. The assessment must be conducted by an appropriately qualified investigator listed on the Form FDA 1572. The ECOG performance status will be recorded in the subject's medical record and on the CRF.

6.3.5 Imaging

Subjects must have a bone scintigraphy test (bone scan) or Na-F PET or C11 acetate PET and CT scan of the abdomen and pelvis within 56 days prior to registration. If a bone scan is used, solitary lesions or lesions which could be attributed to causes other than metastatic prostate cancer must be confirmed with a second modality (i.e., CT or MRI).

When available, standard of care scans will be used to demonstrate metastatic disease at screening. If scans meeting the eligibility criteria are not available, scans may be obtained

during the screening phase. If post-screening radiographic imaging is performed per standard of care to assess disease progression, the same modalities used at screening should be used.

6.4 Safety Assessments

Safety assessments will be performed in conjunction with all visits as indicated in Table 1.

6.4.1 Adverse Events and Serious Adverse Events

Adverse events, including serious AEs (SAEs), seizures, and CVEs will be assessed at all visits and as needed during the course of the study.

All nonserious AEs and SAEs, regardless of relationship to study treatment, will be collected from registration through the post-treatment visit and will be recorded in the subject's medical record and on the CRF. Following the post-treatment visit, only new treatment-related AEs and SAEs will be recorded. Seizures and CVEs (regardless of causality) will be recorded throughout the study.

Only treatment-related AEs, SAEs, seizures, and CVEs (regardless of causality) ongoing at the time of the post-treatment visit will be followed by the investigator until resolution, return to baseline, or a determination by the investigator that no further improvement is expected.

See Section 7.0 for information regarding AE and SAE reporting.

6.4.2 Cerebrovascular Events

Cerebrovascular events that occur at any time during the study, regardless of causality, severity, or outcome, will be recorded in the subject's medical record and on the CRF.

Cerebrovascular events will include all strokes, both ischemic and hemorrhagic in etiology, intracranial hemorrhage and transient ischemic attacks. Transient ischemic attacks are defined as episodes of focal neurologic deficit that resolve within 24 hours.

See Section 7.3.2 for information regarding reporting of CVEs.

6.4.3 Seizures

Seizures that occur at any time during the study, regardless of causality, severity, or outcome, will be recorded in the subject's medical record and on the CRF.

See Section 7.3.3 for information regarding reporting of seizures.

6.5 Concomitant Medications

The subject's current prescription and nonprescription medications will be reviewed at the screening visit and recorded in the subject's medical record and on the CRF. Medications taken from registration through the post-treatment visit will also be recorded. Any medications associated with a possible or probable treatment-related AE will be recorded on the CRF, regardless of when they are taken. The concomitant medication administered, indication, dose, route, frequency, and start and stop dates will be recorded in the subject's medical record and on the CRF.

6.5.1 Anticancer Therapies

All anticancer therapies received prior to screening and through the end of the LTFU phase will be recorded in the subject's medical record and on the CRF. Anticancer therapies include, but are not limited to, radiation, chemotherapy, hormone therapy, investigational cancer therapies, all other systemic therapies, and surgery.

6.5.2 First Cancer-Related Opioid Use

Each subject's first cancer-related opioid use, as determined by the investigator, will be recorded in the subject's medical record and on the CRF. Cancer-related opioid use is defined as use for cancer-related pain that is of at least 2 consecutive days in duration.

Opioid analgesic use for treatment or prevention of infusion reactions, such as chills or rigors, post-procedural pain, or for indications clearly unrelated to cancer pain (e.g., cough, pain due to an injury or accident) should NOT be considered cancer related.

6.6 Survival Status

Confirmation of survival status will be obtained by speaking directly with the subject on the telephone or in person. Death certificates will be obtained as a source document for the date and cause of death recorded on the CRF.

If a death certificate cannot be obtained, one or more of the following documents (in preferential order) will be the source document for the date and cause of death:

1. SSDI/NDI (date of death only).
2. Hospital report.
3. Hospice report.
4. Clinical chart note.

5. Other medical records.

6.7 Laboratory Test Assessments

At the times noted in Table 1, blood samples will be obtained for assessment of the parameters presented in Table 2.

Table 2: Clinical Laboratory Tests

Hematology	**Chemistry**
hemoglobin	sodium
hematocrit	potassium
erythrocyte count	bicarbonate
mean corpuscular volume	chloride
mean corpuscular hemoglobin	lactate dehydrogenase
mean corpuscular hemoglobin concentration	blood urea nitrogen
leukocytes	creatinine
neutrophils	phosphorus
	calcium
lymphocytes	magnesium
monocytes	glucose
eosinophils	albumin
basophils	total protein
platelets	globulin
cell morphology	total bilirubin
	alkaline phosphatase
	alanine aminotransferase
	aspartate aminotransferase
Other Assessments	
total testosterone	
prostatic specific antigen	
serum prostatic acid phosphatase	
Coagulation	
prothrombin time	
international normalized ratio	
Serology	
human immunodeficiency virus	

All clinical laboratory samples will be sent to a central laboratory for testing.

6.8 Immune Monitoring Assessments

Immune monitoring samples will be obtained at the times outlined in Table 1.

Neither the subject nor the investigator will receive results from immune monitoring assessments.

6.8.1 Immune Response

Cellular and immune responses will be assessed from 100 mL blood samples (9x10 mL heparin whole blood tubes and 1x10 mL serum tube) collected at the times noted in the Schedule of Assessments (Table 1). Following infusion of sipuleucel-T, a 10 mL blood sample (1x10 mL serum tube) will be collected.

Immune response assessments will include T cell IFN-γ ELISPOT response to PA2024 and PAP, T cell proliferation response to PAP by tritiated thymidine uptake, humoral response to PA2024 and PAP by ELISA, and chemokine and cytokine production via Luminex assay.

6.8.2 Sipuleucel-T Lot Release

Prior to infusion, small samples (3% to 4%) of cellular components from pre and post-culture (PA2024) cells will be used to assess product potency as part of the normal sipuleucel-T manufacturing process.

Sipuleucel-T lot release assessments will include total nucleated cell (TNC) count, CD54+ cell count and CD54 upregulation.

6.8.3 Product Characterization

Unused portions of the pre and post-culture samples collected for sipuleucel-T lot release will be used for additional analyses including flow cytometry, protein array, and spectral analyses, to identify potential biomarkers of the immune response. Tests to determine cellular composition will include assessment of the activation status of T cells, B cells, and NK cells. In addition, the amounts and types of cytokines produced during the manufacture of sipuleucel-T will also be profiled.

Human leukocyte antigen phenotyping will be performed in order to profile the major histocompatibility complex for each subject, which will make certain immune response analyses possible, such as tetramer analysis (Altman 2006).

6.8.4 Immune Gene Expression Analyses

Castrate-resistant prostate cancer (CRPC) is a heterogeneous disease, with varying symptoms and overall survival ranging from several months to several years (Scher 2011). The ability to accurately predict outcome in men with CRPC is a crucial element in understanding response to treatment. While many studies have correlated clinical and laboratory variables with survival, the role that the immune system plays in controlling prostate cancer has not been fully studied, mainly due to the complexity of the immune system. Moreover, immune response assays can only interrogate discrete pathways 1 at a time, rather than assess the complex interaction between the various cellular and secreted components that comprise the entire immune system. Recent studies (Ross 2012, Olmos 2012) have shown that gene-expression profiling of peripheral blood cells can yield prognostic information with regards to control of CRPC.

An integrated and standardized system for collection, transport, and storage of whole blood specimens and isolation of either ribonucleic acid (RNA) or genomic deoxyribonucleic acid (DNA) (e.g., PAXgene®), will allow analyses of immune gene expression by detection of RNA or genetic analysis of germline DNA.

At screening, an 8.5 mL blood sample will be collected for baseline immune genetic analysis in a specialized tube that stabilizes intracellular DNA (e.g., PAXgene® Blood DNA Tube).

At all immune monitoring assessment time points, a 2.5 mL blood sample will be collected to assess immune gene expression profiles through analysis of intracellular RNAs in immune cells. These blood samples will be collected in a specialized tube containing an additive that stabilizes intracellular RNA (e.g., PAXgene® Blood RNA Tube).

Neither the subject nor the investigator will receive results from gene expression analysis.

6.8.5 Sample Retention

Samples from subjects who do not provide consent for additional optional research (Section 6.8.6) will be retained for up to 5 years following Dendreon's completion of the trial and then will be destroyed.

6.8.6 Additional Optional Research

Subjects will be given the opportunity to allow Dendreon to retain their blood samples (obtained for immune response, lot release, product characterization, and gene expression analysis) indefinitely and to use them for other testing. No additional blood draws will be required beyond those already being collected as part of the study. Additional research may include genetic testing and retained samples may be sent to outside laboratories for testing.

Retained samples will be used for research only, will not be sold, and will not be identified using subject names or other personal identifiers. Neither the subject nor the clinical trial site will receive results from additional testing.

6.9 Study Materials

The clinical trial site will have a calibrated scale for recording body weight and a calibrated sphygmomanometer and thermometer for vital signs assessments. A current and fully stocked advanced cardiac life support cart will be immediately available on the premises. The clinical trial site will also have a refrigerated centrifuge, a monitored and alarmed refrigerator, and a freezer (-20°C or below) as well as containers and dry ice for shipment of blood samples.

The clinical trial site will provide all materials required for accurate documentation of subject visits and study activities.

Dendreon will provide an approved protocol and any required amendments or administrative letters, as well as the IB and electronic CRFs. Materials needed for the collection of laboratory samples, including immune monitoring samples, will be provided by Dendreon. Dendreon will also provide all applicable study specific training materials and reference binders.

7.0 ADVERSE EVENTS

An AE is defined as any untoward medical occurrence in a subject while on study that does not necessarily have a causal relationship with the treatment. An AE can, therefore, be any unfavorable and unintended sign (e.g., abnormal laboratory finding), symptom, or disease temporally associated with the treatment, whether or not considered related to the treatment. Adverse events include exacerbation of a pre-existing illness, an increase in frequency or intensity of a pre-existing episodic event or condition, a condition detected or diagnosed after product administration (even though it may have been present prior to the start of the study) or a continuous persistent disease or symptoms present at screening that worsen following the start of the study.

7.1 Categories for Ranking Severity of Adverse Events

The NCI CTCAE (NCI 2010) will be used to score AE severity. In general, the following general severity definitions apply:

Mild (Grade 1): The AE results in mild, easily tolerated symptoms, or is asymptomatic with clinical or diagnostic observations only. Intervention is not usually indicated.

Moderate (Grade 2): The AE produces moderate symptoms with discomfort sufficient to interfere with some aspect of the subject's normal daily activity. Minimal, local, or noninvasive intervention is required.

Severe (Grade 3): The AE is medically significant but not immediately life threatening, results in discomfort or disability which is incapacitating and prevents most normal daily activities, clearly damaging to the health, requiring hospitalization, prolongation of existing hospitalization or complicated treatment.

Life Threatening (Grade 4): The AE could reasonably result in death unless immediate medical intervention is undertaken.

Fatal (Grade 5): The AE results in death.

7.2 Relationship of Adverse Events to Study Treatments

The following categories will be used to determine relatedness of AEs to study treatments:

None: The AE is clearly related to other factors, such as the subject's clinical state, environmental factors, or other modes of therapy or concomitant medications administered to the subject.

Possible: The AE follows a reasonable temporal sequence from administration of study treatment, but could readily have been produced by the subject's clinical state, environmental factors, or other modes of therapy or concomitant medications administered to the subject.

Probable: The AE follows a reasonable temporal sequence from administration of study treatment and cannot readily have been produced by the subject's clinical state, environmental factors, or other modes of therapy or concomitant medications administered to the subject.

7.3 Serious Adverse Events

An SAE is defined as any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life threatening adverse drug experience, subject hospitalization or prolongation of an existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. An important medical event that may not result in death, be life threatening, or require hospitalization may be considered a SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention

to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse.

7.3.1 Serious Adverse Event Collection and Reporting

All SAEs reported or observed, regardless of relationship to study treatments, and any remedial action(s) required, will be collected at all visits from registration through the post-treatment visit. Only treatment-related SAEs, seizures, and CVEs (regardless of causality) ongoing at the time of the post-treatment visit will be followed by the investigator until resolution, return to baseline, or the investigator determines no further improvement is expected. Only new treatment-related AEs and SAEs, seizures, and CVEs (regardless of causality) will be collected after the post-treatment visit.

All SAEs, whether or not considered related to study treatment, must be reported to Dendreon within 24 hours by entering the information on the electronic SAE report form. If access to the electronic SAE Form is unavailable for any reason, the SAE information must be reported to Dendreon or its designee within 24 hours by phone or by facsimile using the hardcopy SAE report form.

Dendreon Corporation	
Attn:	Safety Manager
Facsimile:	(206) 829-1647
Phone:	(206) 219-7189
After Hours:	(206) 274-6774

Significant new information regarding an ongoing SAE and the resolution must be sent to Dendreon within 3 business days of awareness of the new information on either the electronic or hardcopy SAE report form.

The principal investigator is responsible for notifying the relevant IRB of any SAE that occurs in a subject participating at their clinical trial site and any Investigational New Drug (IND) Safety Reports issued by Dendreon unless otherwise instructed by relevant IRB policy.

7.3.2 Cerebrovascular Events

All CVEs, regardless of causality, severity, or outcome, will be reported as AEs and SAEs when they occur from registration until the subject ceases study participation.

7.3.3 Seizures

All seizures, regardless of causality, severity, or outcome, will be reported as AEs and SAEs when they occur from registration until the subject ceases study participation.

7.3.4 Death Reports

Death is an expected outcome of this study. Deaths that meet any of the following criteria must be reported as an SAE:

- Deaths that occur within 30 days of receiving the last study treatment.
- Deaths that are the outcome of a SAE that occurs within 30 days from the last study treatment and are not due to disease recurrence.
- Deaths due to a seizure or CVE, regardless of causality, that occur at any time during the study.
- Deaths that occur at any time during the study and are considered by the investigator to be possibly or probably related to the study treatment.

Deaths that do not meet these criteria will not be reported as an SAE, but will be recorded on the CRF.

7.3.4.1 Expedited Reporting Requirements

Dendreon will notify the FDA and all participating principal investigators of any AE associated with the use of study treatments that is serious, unexpected and at least possibly related. Such notification will be provided within 15 calendar days after Dendreon's initial receipt of the information. If the event was fatal or life threatening, FDA will be notified no later than 7 days after Dendreon's initial receipt of the report.

The FDA will be notified of all deaths occurring within 30 days of sipuleucel-T infusion, regardless of causality, via a written IND Safety Report.

Serious AEs that are attributable to disease progression will be considered expected, and, therefore, will not be reported by Dendreon on an expedited basis.

7.4 Laboratory Test Result Abnormalities

The following laboratory abnormalities should be captured on the AE CRF or SAE Report Form as appropriate:

- Any clinically significant result that is not part of another reported clinical diagnosis.
- Any result that meets the definition of an SAE.
- Any result leading to study drug discontinuation or interruption.
- Any result that required therapeutic intervention or a change in subject management.

Laboratory abnormalities not meeting the above conditions will not be reported on the AE CRF or SAE report form.

7.4.1 Safety Monitoring and Enrollment Suspension

An internal Data Monitoring Committee (DMC) will be notified within 48 hours of AEs with an outcome of death and nonfatal AEs with Grade ≥ 3 toxicity and that are at least possibly related to the study treatment. Consideration will be given to suspending enrollment to an arm for any of the following:

- An AE with an outcome of death which is at least possibly related to the study treatment(s).
- The occurrence of nonfatal AEs with Grade ≥ 3 toxicities (with the exception of Grade 3 chills, pyrexia, fatigue, or asthenia) which are at least possibly related to study treatment(s) in more than 3 of the first 10 subjects enrolled in an arm, or in more than 30% of subjects in an arm at any time beyond enrollment of 10 subjects in that arm.

If enrollment is suspended in either arm, study treatments will be discontinued in all subjects meeting any of the criteria for stopping treatment (Section 4.3), but may be continued in all other subjects. Enrollment to the suspended arm will resume only with concurrence of the DMC and FDA.

8.0 STATISTICAL CONSIDERATIONS

8.1 General Considerations

This Phase 2 randomized, open-label study is designed to assess the effects of sipuleucel-T when administered concurrently or sequentially with enzalutamide. Subjects will be randomized 1:1 to either the concurrent arm or the sequential arm, stratified by PSA levels (≥ 25 ng/mL, yes or no) and LDH levels (≥ 200 IU/L, yes or no). In general, data will be summarized in aggregate and by treatment arm. All statistical tests will be performed at the 2-sided 0.05 significance level

unless otherwise noted. Nominal p-values will be provided with no multiplicity adjustment for secondary or exploratory endpoints.

8.2 Sample Size Determination

The study is designed to test the null hypothesis of no difference between the treatment arms for immune response over time evaluated using PA2024-stimulated T cell proliferation via tritiated-thymidine uptake. The PA2024 proliferation responses over time will be compared between the concurrent arm and sequential arm using a repeated measurement analysis. With 43 subjects per treatment arm (concurrent and sequential), there is 90% power to detect a 2.0 fold difference in mean response between the arms at any time point assuming a coefficient of variation of 1.25. To allow for drop-outs and subjects who may not receive 3 infusions of sipuleucel-T or at least 10 weeks of enzalutamide, 50 subjects per arm will be enrolled. Coefficients of variation for proliferation responses ranging from 0.69 to 1.40 depending on visit have been observed in a recent trial of sipuleucel-T in a similar population (data on file).

8.3 Populations for Analyses

The immune response population will be defined as subjects who receive 3 infusions of sipuleucel-T and 10 or more weeks of enzalutamide. Analysis of immune response endpoints, including the primary endpoint, will be performed using this population. This population will also be used to perform supplementary analyses of nonimmune response efficacy endpoints.

The intent-to-treat (ITT) population is defined as all randomized subjects, regardless of whether they received treatment. Analysis of nonimmune response efficacy endpoints will be performed using this analysis population.

The safety population will include all subjects who receive at least 1 leukapheresis procedure or receive at least 1 dose of enzalutamide. All safety variables (e.g., AEs, laboratory data, and vital sign data) will be analyzed based on the safety population.

8.4 Endpoints

8.4.1 Primary Endpoint(s)

The primary endpoint is peripheral PA2024-specific T cell immune response to sipuleucel-T over time as measured via a T cell stimulation index from a proliferation assay. This endpoint was selected because it has demonstrated the highest signal to noise ratio of all the T cell assays Dendreon has evaluated in prior studies of sipuleucel-T (data on file).

8.4.2 Secondary Endpoint(s)

Immune responses over time for ELISPOT and ELISA are secondary endpoints as are peripheral PAP-specific T cell immune response to sipuleucel-T over time via a T cell stimulation index from a proliferation assay, and cytokine production by Luminex assay. Additionally, responder analyses by time point will be performed for the data generated from the proliferation assays, ELISPOT, and ELISA. A positive response will be defined as having a post-baseline result exceeding a threshold value, determined on the basis of baseline and historical sipuleucel-T data, that ensures a sufficiently low false positive rate (i.e., 5% or less) for each immune response parameter. The threshold will be antigen and assay dependent.

Time to PSA progression is defined as: 1) the time from randomization to PSA progression, and 2) the time from first enzalutamide treatment to PSA progression. Those subjects who do not experience PSA progression will be censored in the analysis at the date of their last PSA assessment. PSA progression, based on the randomization date (i.e., definition 1) will be defined for those subjects who experience a decline in PSA compared to baseline as the date that a 25% or greater increase in PSA and an absolute increase of 2 ng/mL or more from the nadir is documented, which is confirmed by a second value obtained 3 or more weeks later (Scher 2008). For those subjects who do not experience a decline in PSA compared to baseline, PSA progression is defined as the date a 25% or greater increase from the baseline value along with an increase in absolute value of 2 ng/mL or more after 12 weeks of enzalutamide treatment (Scher 2008). PSA progression based on the first enzalutamide treatment (i.e., definition 2) will be defined in a similar manner except the most recent PSA value prior to the first enzalutamide treatment will be used as the baseline value.

PSA progression time, based on the randomization date, will be calculated as follows for those subjects with PSA progression:
Progression time (days) = [(PSA progression date) – (randomization date)] + 1.

PSA progression time, based on the randomization date, will be calculated as follows for subjects who are censored:
PSA progression time (days) = [last PSA assessment date – (randomization date)] + 1.

PSA progression time based on the first enzalutamide treatment will be defined in a similar manner except the first enzalutamide treatment date will be used instead of the randomization date.

Overall survival is defined as the time from randomization to death due to any cause. Those subjects alive at the time of database cut-off or lost to follow-up will be censored in the analysis at the earlier of the cut-off date or the day of their last documented visit or contact date.

Overall survival time will be calculated as follows for subjects who died prior to data cut-off:
Survival time (days) = [(death date) – (randomization date)] + 1.

Overall survival time will be calculated as follows for subjects who are censored:
Survival time (days) = [(last contact date) – (randomization date)] + 1.

8.4.3 Exploratory Endpoint(s)

The time to next anticancer intervention is defined as the time from randomization to the first anticancer intervention. Those subjects without an anticancer intervention will be censored at their last follow-up assessment when anticancer therapy information is collected.

The time to first opioid use for cancer-related pain is defined as the time from randomization to the first use of an opioid for cancer-related pain. Those subjects without a record of opioid use for cancer-related pain will be censored at their last follow-up assessment when opioid use for cancer-related pain is collected.

The time to first ECOG performance status decline (i.e., increase in numerical value of ECOG performance status) is defined as the time from randomization to the first decline in ECOG performance status by 1 point or more. Those subjects without an ECOG performance status decline will be censored at their last follow-up assessment for ECOG performance status.

8.5 Analyses

8.5.1 Subject 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 infused.
- Number of subjects who prematurely discontinued the study (i.e., refused further study assessments [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 immune response and safety analysis sets.

In addition, the number of subjects screened for the trial will be summarized for the overall study population.

8.5.2 Demographics and Baseline Characteristics

Demographic information and baseline disease information and characteristics will be summarized with descriptive statistics for all analysis populations and compared between treatment groups using the Wilcoxon test for continuous variables and Fisher's exact test for categorical variables.

8.5.3 Efficacy Analyses

The primary efficacy analysis will consist of a repeated measurement analysis of immune response over time evaluated using PA2024-stimulated T cell proliferation via tritiated-thymidine uptake based on the immune response population. The logarithm of response will be used for analysis. Fixed effect terms in the model will include treatment arm, visit as a class effect, and treatment by visit interaction. The correlation of responses across time within a subject will be modeled using several candidate variance-covariance structures including unstructured, compound symmetry, heterogeneous compound symmetry, autoregressive (1), and heterogeneous autoregressive (1). The variance-covariance structure providing the smallest Bayesian information criteria will be selected for the final model. Fixed effect terms in the model will be tested for significance using type III sums of squares. The formal test for difference between the treatment arms will be based on the p-value for the treatment arm effect unless a significant treatment by visit interaction ($p < 0.05$) is observed, in which case by-visit treatment comparisons will be made using appropriate contrast statements. Estimates of treatment effect and corresponding 95% confidence intervals (CIs) will be provided on the ratio scale obtained by exponentiation of the model derived treatment effect and CI on the logarithm scale. Immune responses over time for other assays will be analyzed using identical methods described for the primary efficacy analysis except for the ELISPOT, which will be analyzed using ranks instead of on the logarithm scale.

The response rate for each assay and for each antigen will be compared between treatment arms at each visit using Fisher's exact test based on the immune response population. In addition, analyses will be performed modeling response rates over time using appropriate methods to account for the correlation of responses over time within a subject.

Time to PSA progression will be compared between the treatment arms using a Cox regression model with terms for treatment, baseline PSA (logarithm scale), and baseline LDH (logarithm scale) in the model based on the ITT population. The estimated HR of the treatment effect and

its 2-sided, 95% CI, using the sequential arm as the denominator will be provided. The percentage of subjects free of PSA progression with an associated 95% CI at landmark time points such as 6 and 12 months will be provided by treatment arm as well as pooled over treatment arms using the Kaplan-Meier method.

Overall survival, time to next anticancer intervention, time to first chemotherapy, time to first cancer-related opioid use, and time to first ECOG performance status decline will be analyzed in a similar manner as described for time to PSA progression.

8.5.4 Safety Analyses

Safety data will be summarized descriptively in aggregate and by treatment group within the safety population. No formal statistical testing is planned for the safety data.

8.5.4.1 Adverse Events

Adverse events will be summarized and listed by treatment arm and by the Medical Dictionary for Regulatory Activities (MedDRA) terms, by preferred term within each system organ class. Summary tables will include all AEs reported in the treatment arms from the first leukapheresis or enzalutamide dose. Summaries to be produced include the following:

- Incidence within system organ class (MedDRA).
- Incidence by decreasing frequency.
- Incidence by NCI CTCAE severity grade, by decreasing frequency.
- Incidence of Grade ≥ 3 AEs, by decreasing frequency.
- Incidence of SAEs.
- Incidence of AEs within 1 day of infusion.
- Incidence of AEs that resulted in premature discontinuation of study treatments.

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 greatest severity for an AE occurring multiple times for a subject will be counted.

8.5.4.2 Laboratory Data

Summaries of laboratory data collected from baseline until study completion will include:

- Incidence of clinically significant laboratory abnormalities by NCI CTCAE Version 4.03 (NCI 2010). A clinically significant laboratory toxicity is defined as a post-baseline grade 3 or higher toxicity where the baseline value was grade 2 or lower.

- Summary statistics (mean, median, standard deviation, minimum, and maximum) for laboratory values and their change from baseline by time point.

Baseline results will be defined as the most recent nonmissing value obtained on or prior to the randomization date.

8.5.4.3 Vital Signs

Vital sign data (blood pressure, respiration rate, heart rate, and body temperature) will be summarized descriptively by time point.

8.5.5 Study Treatment Administration

Leukapheresis and sipuleucel-T infusion information will be summarized by treatment group. This will include the following:

- Number of subjects who received a total of 0, 1, 2, or 3 infusions.

- Reason(s) for not completing 3 infusions.

- Number of subjects who receive a total of 0, 1, 2, 3, 4, or 5 or more leukaphereses.

- Number of subjects who receive a total of 3 leukaphereses and 3 infusions.

The duration of treatment with enzalutamide will be summarized by treatment group. The percent compliance with enzalutamide treatment will be computed as the number of pills taken divided by the expected number of pills to be taken and will be summarized by treatment group.

8.5.6 Concomitant Medications and Procedures

Concomitant medications and procedures will be presented in data listings by treatment group and will be coded using the World Health Organization Drug Dictionary. A summary table will be provided by treatment group and for all subjects combined. Separate summaries will be provided for medications that were started prior to randomization and for medications started after randomization.

8.5.6.1 Other Analyses

Use of select anticancer treatments during the study will be summarized by treatment group. This summary will include types of therapies used and will be based on the ITT population.

Data from sipuleucel-T lot release assessments will be summarized. Data to be summarized include CD54 upregulation, CD54+ cell count, and TNC count. These data will be summarized descriptively by infusion (1, 2, and 3) and cumulative (summed across infusions). Cumulative lot release assessment data will be compared between both arms using a t-test on the logarithm scale based on the immune response analysis population.

Prostate specific antigen data, including change from baseline, will be summarized descriptively by treatment arm at each time point for the ITT population. Additionally, the maximal decline of serum PSA from baseline at any time point will be summarized using waterfall plots. Baseline will be defined as the value collected immediately prior to the registration PSA value. Additional analyses of PSA will be performed using the most recent PSA value prior to the initiation of enzalutamide as the baseline value.

8.6 Interim Analyses

No formal interim analysis will be performed in this study. For this open-label study, descriptive summaries of safety assessments and immune response parameters may be generated on a periodic basis.

9.0 REGULATORY REQUIREMENTS

9.1 Pre-Study Documentation

The principal investigator will sign and return to Dendreon the Protocol Signature Page for the original protocol and each amendment, if applicable, and provide current medical licenses, curriculum vitae, and the Form FDA 1572 Statement of Investigator. All forms must be updated as applicable throughout the study.

Dendreon must receive the following documentation prior to study initiation:

- Signed Protocol Signature Page.
- FDA Form 1572 signed by the principal investigator.
- Curriculum vitae of the all investigators listed on Form FDA 1572, updated within the past 2 years.

- Copies of current medical licenses for all investigators listed on Form FDA 1572.
- Financial disclosure forms for all investigators listed on Form FDA 1572.
- Copy of the IRB approval letter for the study.
- Copy of the IRB-approved ICF.
- IRB membership list or Department of Human and Health Services Assurance Number.

9.2 Investigator Obligations

The principal investigator will ensure all clinical trial site personnel, including sub investigators, conduct the study in compliance with the Declaration of Helsinki the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP) and the FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (FDA 2005). The investigator will follow all national, state, and local laws.

The principal investigator will be responsible for the subject's compliance to the study protocol, and must meet periodically with the Dendreon study monitor.

All investigators listed on Form FDA 1572 must complete financial disclosure forms (including information on spouses, legal partners, or dependent children) before study initiation. Investigators must promptly update this information if any relevant changes occur in the course of the study or in the year after the study is completed (21 CFR §54.4). Investigators must also complete a new financial disclosure form annually throughout the study, regardless of whether any information has changed.

In addition, the principal investigator is responsible for providing Dendreon an adequate final report shortly after study participation is complete, in accordance with 21 CFR §312.64.

9.3 Institutional Review Board

The investigator is responsible for ensuring that this protocol and relevant supporting data are submitted to the appropriate Institutional Review Board (IRB) for review and approval before the study is initiated. Dendreon must receive a letter documenting the IRB approval prior to initiation of the study. Amendments to the protocol will also be submitted to, and approved by, the IRB prior to implementation of any change(s). The investigator is also responsible for informing the IRB of the progress of the study and for obtaining annual IRB renewal. The IRB must be informed by the investigator when the study is complete and should be provided with a summary of the results of the study as required by the IRB.

9.4 Informed Consent

The investigator is responsible for ensuring that all subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding this study, including their right to withdraw at any time.

Prior to the initiation of any study procedures, including medication washouts, all subjects must provide written consent on the Informed Consent Form (ICF) indicating their consent to participate. The investigator or an appropriately qualified delegate listed on FDA Form 1572 will provide a full explanation of the study and allow the subject to read the ICF and ask any questions that may arise. The subject will be given sufficient time to properly consider the information and to make an informed decision prior to signing the ICF. The investigator or an appropriately qualified delegate listed on FDA Form 1572 will document the informed consent process in the subject's medical record and will provide a copy of the signed ICF to the subject.

The ICF, including any amendments, must first be reviewed and approved by Dendreon and then by the designated IRB prior to use in the study.

If an amendment to the protocol changes the subject participation schedule in scope or activity, or increases the potential risk to subjects, the ICF will be revised and submitted to the IRB for review and approval. The revised ICF must be used to obtain consent from subjects currently participating in the study if the information is relevant, or per the IRB's instructions. The revised ICF will be used to obtain consent from any new subject who is enrolled in the study after the approval date of the amendment.

9.5 Subject Confidentiality

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. Subjects' individual identifying information will be kept as confidential as possible under local, state, and federal law. Medical information may be given to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated as a result of this study will be available for inspection on request by the FDA, Dendreon or its representatives, or the IRB. Dendreon may retain in its files copies of subject medical information, with subject identifiers redacted.

Individual subject identities will not be disclosed in any report or publication related to the trial, and will not be obtained on any CRFs maintained by Dendreon.

Sipuleucel-T therapy is similar to an autologous blood transfusion; revealing subject identifying information is critical for ensuring subject safety. To maintain the chain of identity and thereby

ensure subject safety, the sipuleucel-T label will contain subject identifying information that will be revealed to Dendreon's apheresis and manufacturing personnel.

10.0 STUDY MANAGEMENT

10.1 Study Documentation

The principal investigator and clinical trial site personnel are responsible for maintaining a comprehensive and centralized filing system containing all study-related documentation. These files must be suitable for inspection by Dendreon, representatives of Dendreon, or the FDA at any time, and should consist of the following elements:

- Copies of completed CRFs.
- Subject files, containing supporting source documentation from the subject's medical record, including laboratory data, pathology reports, and the signed ICF.
- Regulatory files, containing the protocol with all amendments and protocol signature pages, copies of all other required regulatory documentation, and all correspondence between the clinical trial site and the IRB and Dendreon.
- Drug accountability files, containing a complete account of the receipt and disposition of all study treatments.

The investigator shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is so notified.

10.2 Data Collection

Dendreon will provide electronic CRFs for reporting data. All required fields on the CRFs must be completed. All data recorded on CRFs must be supported by original (source) documentation.

10.3 Protocol Compliance

To ensure accurate interpretation and implementation of the study, the procedures and endpoints defined in the protocol will be carefully reviewed by the principal investigator and the clinical trial site personnel prior to the time of study initiation.

Dendreon, after consultation with the principal investigator, will be the final arbiter of eligibility, toxicity, and other endpoints should a difference of opinion exist.

10.4 Monitoring

A representative from Dendreon will visit the clinical trial site periodically to monitor adherence to the protocol, adherence to applicable FDA regulations, and the maintenance of adequate and accurate records. Case report forms will be reviewed to ensure that key safety and efficacy data are reported as specified by the protocol. The Dendreon representative must be permitted to access subjects' complete medical records, laboratory data, and other source documentation as needed to appropriately monitor the trial.

10.5 Quality Assurance

Dendreon Quality Assurance may arrange to visit the clinical trial site to audit the performance of the study and the study documents originating at the site. The audit may be conducted by a Dendreon representative or designee. The principal investigator will be informed of the outcome of the audit.

In addition, inspections by health authority representatives and/or the IRB are possible at any time. The investigator must inform Dendreon of any such inspection immediately.

Direct access to source documentation and subjects' medical records must be provided for audits and inspections.

10.6 Disclosure of Data and Publication

The principal investigator, sub investigators, and other clinical trial site personnel working on the study will submit all proposed publications, papers, abstracts or other written materials related to the study, or an outline of any proposed oral presentation with respect thereto, to Dendreon at least 1 month prior to (i) submission of such written materials for publication, or (ii) any proposed oral disclosure to a third party. Dendreon shall have the right to comment on such written material or outline; such comments shall be considered in good faith by the principal investigator in determining the final form of disclosure. Notwithstanding any of the above, neither the principal investigator nor anyone else working on the study may include any confidential information in any such publication or disclosure.

11.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ADT	androgen deprivation therapy
CI	confidence interval
COI	chain of identity
CPDF	Clinical Cell Product Disposition Form
CRF	case report form
CRPC	castrate-resistant prostate cancer
CT	computed tomography
CVE	cerebrovascular event
CYP	cytochrome P450
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
ELISA	enzyme-linked immunosorbent assay
ELISPOT	enzyme-linked immunospot assay
FDA	Food and Drug Administration
FPL	Final Product Label
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GM-CSF	granulocyte-macrophage colony-stimulating factor
HR	hazard ratio
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
LDH	lactate dehydrogenase
LHRH	luteinizing hormone-releasing hormone
LTFU	long term follow-up
mCRPC	metastatic castrate-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
MRI	magnetic resonance imaging
Na-F	sodium fluoride
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDI	National Death Index
PAP	prostatic acid phosphatase
PBMC	peripheral blood mononuclear cell
PET	positron emission tomography
PSA	prostate specific antigen
RNA	ribonucleic acid
SAE	serious adverse event
SSDI	Social Security Death Index
TNC	total nucleated cells
ULN	upper limit of normal

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APPENDIX 1: EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE CRITERIA

Grade	Performance Criteria	Karnofsky Scale Equivalent
0	Normal activity. Fully active, able to carry on all predisease 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

APPENDIX 2: CHILD-PUGH SCORE

Criteria for Child-Pugh Classification

Score ☐

Grade A = 5-6 Grade B = 7-9 Grade C = 10-15

Clinical and Biochemical Measurements		Points Scored for Increasing Abnormality		
		1	2	3
Hepatic encephalopathy (grade)*	○1 ○2 ○3	None	1 and 2	3 and 4
Ascites	○1 ○2 ○3	Absent	Mild	Moderate
Total bilirubin (mg/dl)	○1 ○2 ○3	< 2.0	2.0 - 3.0	> 3.0
Serum albumin (g/dl)	○1 ○2 ○3	> 3.5	2.8 - 3.5	< 2.8
Prothrombin time (sec. prolonged) or Prothrombin time INR**	○1 ○2 ○3	< 4 or < 1.7	4 - 6 or 1.7 - 2.3	> 6 or >2.3

*According to grading of Trey, Burns, and Saunders (1996).

APPENDIX 3: MEDICATIONS METABOLIZED BY CYTOCHROME ENZYMES

Cytochrome system inducers and inhibitors relevant to enzalutamide:

Strong CYP2C8 inhibitor: gemfibrozil

CYP2C8 inducer: rifampin

Medications metabolized by CYP3A4, CYP2C9, or CYP2C19 that have a narrow therapeutic index:

midazolam	quinidine
warfarin	sirolimus and tacrolimus
omeprazole	phenytoin
alfentanil	s-mephenytoin
cyclosporine	lansoprazole
dihydroergotamine	pantoprazole
ergotamine	esomeprazole
fentanyl	rabeprazole
pimozide	

Strong and moderate CYP3A4 inducers:

carbamazepine	etravirine
phenobarbital	nevirapine
phenytoin	modafinil
oxcarbazepine	nafcillin
rifabutin	pioglitazone
rifampin	troglitazone
rifapentine	glucocorticoids
bosentan	St. John's Wort
efavirenz	

APPENDIX 4: INFUSION GUIDELINES

Preinfusion Procedures

DO NOT OPEN THE CLIMATE-CONTROLLED INNER COMPARTMENT OF THE SHIPPING PACKAGE UNTIL THE INFUSION STAFF IS READY TO INFUSE.

DO NOT INFUSE SIPULEUCEL-T UNTIL YOU RECEIVE WRITTEN APPROVAL SIGNED BY THE IMMUNOTHERAPY MANUFACTURING FACILITY (IMF) QUALITY ASSURANCE (QA) PERSONNEL VIA THE CLINICAL CELL PRODUCT DISPOSITION FORM (CPDF).

Delivery Time Notification

A courier service contracted by Dendreon arranges and provides transportation of sipuleucel-T from the IMF to the clinical trial site infusion center.

When the manufacturing schedule is determined for each subject, Dendreon Clinical Scheduling forwards a Subject Schedule Report to the Clinical Research Coordinator (CRC), indicating the approximate delivery times for all 3 infusions. The CRC is contacted immediately if there is a change in delivery time.

Sipuleucel-T Shipping, Receipt, and Storage

Sipuleucel-T is transported to the infusion center in an insulated polyurethane container. Sipuleucel-T must remain in the original, unopened shipping package, which is designed to maintain sipuleucel-T at 2ºC to 8°C until it is infused. Quality control testing is performed on each sipuleucel-T product. Due to shipping logistics and expiration times, sipuleucel-T is routinely shipped to the infusion center before required QC release testing is complete. Dendreon's QA personnel review the results and issue a written release called the CPDF, indicating whether the sipuleucel-T is "Approved" or "Rejected" for infusion, or if manufacturing was "Terminated" in process.

The CPDF is faxed to the infusion center or pharmacy. Upon receipt, the pharmacy, infusion staff, or CRC completes the section of the CPDF marked "Infusion Site Use Only" and faxes it to Dendreon at the number provided on the form. This notifies Dendreon that the CPDF was received.

If the sipuleucel-T does not meet Dendreon quality specifications and is rejected or terminated, Dendreon Clinical Scheduling contacts the clinical trial site to notify them of the sipuleucel-T

rejection or termination. If necessary, Dendreon Clinical Scheduling arranges for the return to the IMF of any delivered and rejected or terminated sipuleucel-T. Dendreon Clinical Scheduling will also reschedule the subject as necessary. The clinical trial site may also contact the Dendreon medical monitor for additional information regarding a sipuleucel-T rejection or termination.

Subject Preparation for Infusion

It is recommended subjects are premedicated approximately 30 minutes prior to infusion with 650mg acetaminophen orally and an antihistamine such as diphenhydramine 50mg orally.

Obtain the subject's vital signs within 1 to 30 minutes prior to the start of the infusion. Document the subject's blood pressure, heart rate, temperature, and respirations in his medical record.

Sipuleucel-T Inspection and Expiration Time

When the infusion staff and subject are ready for the infusion, open the polyurethane container and inspect the sipuleucel-T and the Final Product Label (FPL) affixed to the sipuleucel-T bag. The sipuleucel-T expiration time is indicated on the CPDF and on the FPL. **The expiration time is noted in the time zone of the infusion center. Contact Dendreon Clinical Scheduling immediately if the expiration times on both documents do not match**. Confirm the infusion will begin prior to the sipuleucel-T expiration time noted on the CPDF and the FPL. If sipuleucel-T administration cannot begin prior to the expiration time shown on the label, **do not infuse** and contact Dendreon Clinical Scheduling for further instructions.

Occasionally, there is a delay in obtaining the CPDF due to operational or technical reasons.

- If Dendreon indicates the CPDF is imminently pending, it is acceptable to administer the recommended premedications 30 minutes prior to the sipuleucel-T expiration time.
- If a CPDF marked "Approved" is obtained within 30 minutes prior to the sipuleucel-T expiration time, it is acceptable to administer the recommended antihistamine intravenously rather than orally, in order to achieve higher systemic concentrations at the time the infusion is initiated.

Two different infusion center staff members must **confirm** the subject identifiers (name, initials, subject number, and lot or chain of identity [COI] number) on the CPDF and FPL match the intended subject. Document this verification process in the subject's medical record. If any information on the CPDF or FPL is incorrect or is inconsistent, contact Dendreon Clinical Scheduling and **do not infuse** the sipuleucel-T until the discrepancy is resolved.

The contents of the sipuleucel-T bag are generally slightly cloudy, with a cream-to-pink color. Examine the sipuleucel-T bag for leakage. Gently re-suspend the contents by slowly rocking the bag back and forth, inspecting for clumps and clots. Small clumps of cellular material should disperse with gentle manual mixing.

If the sipuleucel-T bag leaks or if clumps remain in the bag **do not infuse** and contact the Dendreon Clinical Safety line.

Sipuleucel-T Infusion Supplies

Use a large-bore intravenous (IV) line suitable for blood transfusions to infuse sipuleucel-T; 18- or 20-gauge is recommended, but 22-gauge may be used when necessary. The typical IV tubing set used for sipuleucel-T infusions has a universal spike, a 10-20 drip/mL macro-drip chamber WITHOUT a cell filter, and a minimum of one injection port. An infusion pump may be used, but is not required, to ensure the rate of infusion is controlled.

Infusion Procedures

DO NOT INFUSE SIPULEUCEL-T PRIOR TO RECEIPT OF A CPDF INDICATING SIPULEUCEL-T IS APPROVED FOR INFUSION.

Sipuleucel-T Infusion

Infuse sipuleucel-T over the shortest period that is well tolerated but not less than 60 minutes. Record the infusion start and stop times in the subject's medical record.

If the subject develops an acute infusion reaction, slow the infusion and consult the section below on "Managing Acute Infusion Reactions" for recommendations regarding administration of additional medications. It may not be necessary to immediately discontinue the infusion.

If the infusion of sipuleucel-T is interrupted, do not resume the infusion if the sipuleucel-T bag will be held at room temperature for more than 3 hours following removal from the shipping container. Record all sipuleucel-T infusion re-start and stop times in the subject's medical record.

Adverse Event and Concomitant Medication Documentation

Record all concomitant medications administered to the subject and all AEs.

Document all concomitant medications administered, including all premedications, using the generic drug names, doses, routes, frequencies, indications, and start and stop dates in the subject's medical record.

Describe any AEs, including start and stop dates (and duration if less than 24 hours), whether or not the event was serious, severity (based on the NCI CTCAE), relationship to sipuleucel-T (none, possible, or probable), and the outcome in the subject's medical record.

Refer to Section 7.0 of the protocol for more information regarding AEs and SAEs, including reporting requirements.

Post-infusion Procedures

Subject Follow-up

Observe the subject for at least 30 minutes after the infusion. Obtain vital signs within 30 minutes (± 10 min) after completion of the infusion. Document the subject's blood pressure, heart rate, temperature, and respirations in the subject's medical record.

Documentation

Retain the original CPDF and file it in the subject's medical record.

Sipuleucel-T Return or Disposal

Dispose of the sipuleucel-T bag and tubing according to institutional procedures for disposal of biohazardous waste that contains human blood. Dispose of all packaging materials and gel packs appropriately.

If instructed by Dendreon to return the sipuleucel-T, place the remaining sipuleucel-T in the original shipping box with the packaging materials and ship per Dendreon instructions.

Managing Acute Infusion Reactions

Refer to the current sipuleucel-T IB for a complete list of acute infusion reactions, including severity. Some common acute infusion reactions, such as pyrexia and/or rigors (chills), may warrant slowing of the infusion rate. If acute infusion reactions occur, the current infusion time and subsequent infusion times can be increased up to a total infusion time of 1.5 to 2.0 hours. If the infusion of sipuleucel-T is interrupted, do not resume the infusion if the sipuleucel-T bag will be held at room temperature for more than 3 hours following removal from the shipping container.

For subjects who experience a significant acute infusion reaction, including rigors, during or immediately following an infusion, the following guidelines may be helpful:

1. As prophylaxis during subsequent infusions, the dose or intensity of the recommended premedications may be increased. For instance, acetaminophen may be given at a higher oral dose than used previously and an IV rather than oral antihistamine may be administered. In addition, IV administration of an H_2 antagonist may be considered as an additional premedication.
2. A narcotic such as meperidine may be used as treatment for an AE or as prophylaxis during subsequent infusions.
3. Additional or other premedications may be considered according to institutional practices and/or local standards of care. **Steroids should not be used for premedication or treatment during sipuleucel-T infusions. The use of steroids may suppress any immune response elicited by sipuleucel-T.**
4. For severe acute infusion reactions supportive care measures such as supplemental oxygen, bronchodilator therapy for wheezing, and epinephrine should be used as clinically indicated.

Contact the Dendreon Clinical Safety line at any time during the study for urgent medical concerns.

Dendreon Contact Information

Dendreon Connect

Support for day of infusion issues such as cancellations and delivery or disposition delays.

Email (preferred): dendreonconnect@dendreon.com

Phone (if urgent): (877) 340-3844

Dendreon Clinical Scheduling

Support for scheduling related issues.

Email (preferred): clinicalscheduling@dendreon.com

Phone: (206) 219-7218

Dendreon Clinical Safety Line

Support at any time during the study for urgent medical concerns.

Phone: (206) 274-6774