Clinical Protocol

IMMUNE MONITORING PROTOCOL IN MEN WITH PROSTATE CANCER ENROLLED IN A CLINICAL TRIAL OF SIPULEUCEL-T

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PROTOCOL NUMBER:	P11-4
STUDY PRODUCT:	Provenge® (sipuleucel-T)
ORIGINAL PROTOCOL ISSUE DATE:	17 MAY 2012
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STUDY SPONSOR:	Dendreon Corporation 1301 2nd Avenue Seattle, WA 98101

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CONFIDENTIALITY STATEMENT

PROTOCOL SIGNATURE PAGE

IMMUNE MONITORING PROTOCOL IN MEN WITH PROSTATE CANCER ENROLLED IN A CLINICAL TRIAL OF SIPULEUCEL-T

Original Protocol Issue Date: 17 MAY 2012

Amendment 1.0 Issue Date: 11 SEP 2013

By signing below, the Principal Investigator agrees to adhere to the protocol as outlined.

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PROTOCOL SYNOPSIS

Protocol Title: Immune Monitoring Protocol in Men with Prostate Cancer Enrolled in a Clinical Trial of Sipuleucel-T

Protocol Number: P11-4

IND Application Number: BB-IND 6933

Clinical Phase: Phase 4

Product, Dosage Form, Route, and Dose Regimen: Provenge® (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), which have been activated during a defined culture period with a recombinant human protein. The recombinant human protein, PA2024, is composed of prostatic acid phosphatase (PAP) linked to granulocyte-macrophage colony-stimulating factor (GM-CSF), an immune cell activator.

Each dose of sipuleucel-T is prepared using cells from a single leukapheresis procedure. A complete course of sipuleucel-T therapy consists of 3 doses of sipuleucel-T administered via intravenous (IV) infusion at approximately 2-week intervals.

Reference Product, Dosage Form, Route, and Dose Regimen: No reference product will be used in this study. Subjects may receive a reference product as part of the Dendreon-sponsored trial or registry, or investigator-initiated trial (IIT), in which they are concurrently enrolled.

Primary Objective: To evaluate the immune response induced by sipuleucel-T

Exploratory Objectives:

- Where overall survival (OS) data are collected in the concurrent Dendreon-sponsored trial or registry, to evaluate the relationship between OS and immune response
- To explore the relationships between sipuleucel-T product parameters (APC activation, APC count, and total nucleated cell [TNC] count) and immune response
- To explore relationships between OS and genomic or gene expression profiles

Primary Endpoint: The percentage of subjects who exhibit any immune response at any post-treatment time point (6, 10, 14, 26, 39, and 52 weeks after the first infusion of sipuleucel-T) on the basis of:

- Interferon-gamma (IFNγ) enzyme-linked immunospot (ELISPOT) response to PAP or PA2024
- T cell proliferation response to PAP or PA2024
- Anti-PAP or anti-PA2024 humoral response

Exploratory Endpoint:

- Characterization of genomic or gene expression profiles

Study Design and Duration:

This study (P11-4) is a multicenter trial in men ≥18 years of age with prostate cancer who are enrolled in a Dendreon-sponsored trial or registry, or IIT and will receive sipuleucel-T. Men who meet these criteria and have not yet undergone leukapheresis for their first dose of sipuleucel-T are eligible to participate in P11-4. Subject accrual and study duration for P11-4 will depend on the timing and population of the concurrent trials.

For P11-4, cellular and humoral immune responses will be assessed from 60-mL blood samples (immune monitoring blood samples; 5x10 mL heparin whole blood tubes and 1x10 mL serum tube) obtained at baseline (defined for the purposes of P11-4 sample collection as any time after informed consent, but prior to leukapheresis for the first dose of sipuleucel-T), as well as 6, 10, 14, 26, 39, and 52 weeks after the first infusion of sipuleucel-T.

As part of the normal manufacturing and quality control process, samples of cellular components from pre-culture and post-culture (sipuleucel-T) cells are used to confirm product quality attributes and potency (product characterization). Participation in this study will allow unused portions of these pre- and post-culture samples, an additional 1% of the pre-culture cellular components, and immune monitoring blood samples to undergo additional analyses (e.g., flow cytometry or spectral analyses) to identify potential biomarkers of the immune response.

Subjects in this trial will be given the opportunity to consent to allow Dendreon to collect investigational blood samples for use in additional optional research (AOR), which will include both genomic and gene expression analyses, and other additional testing (e.g., human leukocyte antigen [HLA] phenotyping or protein array). Blood samples for AOR will be collected from only those subjects who agree to allow Dendreon to conduct these analyses. For genomic analyses, an additional, 8.5-mL blood sample will be collected in a specialized tube containing an additive that stabilizes DNA (e.g., PAXgene® Blood DNA tube) one time only, either at baseline (preferred) or at any one of the other immune monitoring time points (6, 10, 14, 26, 39, or 52 weeks after the first infusion of sipuleucel-T). For gene expression analyses, an additional,

2.5-mL blood sample will be collected in a specialized tube containing an additive that stabilizes RNA (e.g., PAXgene Blood RNA tube) at the same time points as immune monitoring (baseline and 6, 10, 14, 26, 39, and 52 weeks after the first infusion of sipuleucel-T).

Post-baseline blood sampling for immune monitoring and AOR will be performed only in subjects who receive at least 1 partial infusion (>0 mL) of sipuleucel-T; subjects who do not receive at least 1 partial infusion of sipuleucel-T will no longer participate in this study.

Participation in this study will end following collection of the week 52 blood sample(s); when the subject no longer wishes to participate; or if the subject withdraws from, or otherwise completes participation in, the study in which the subject is concurrently enrolled. After completion of this study (either through completion of all study visits or early withdrawal), subjects will continue to be followed per the schedule noted in the protocol in which they are concurrently enrolled.

For subjects who consent to participate in P11-4, samples obtained for product characterization, immune monitoring, and other testing will be retained for up to 5 years following Dendreon's completion of this trial and then destroyed, except for subjects who provide additional consent for AOR.

For P11-4 subjects who provide additional consent for AOR, Dendreon or its designee may retain samples obtained for product characterization, immune monitoring, AOR, and other additional testing indefinitely.

For subjects concurrently enrolled in a Dendreon-sponsored trial or registry, neither the subject nor the trial site will receive immune monitoring, AOR, or other test results. For subjects concurrently enrolled in an IIT, test results will be provided to the Principal Investigator or site for research purposes only and only as pre-specified in the approved IIT protocol. For these subjects, test results will not be released for clinical use, or for any use not specified in the approved IIT protocol.

Study Population: Subjects who are enrolled in a Dendreon-sponsored trial or registry, or IIT, and will receive sipuleucel-T, but have not undergone leukapheresis for their first dose of sipuleucel-T, are eligible to participate in this study.

Statistical Considerations: The primary endpoint is the percentage of subjects who exhibit any immune response at any post-treatment time point (6, 10, 14, 26, 39, and 52 weeks after the first infusion of sipuleucel-T). Logistic regression will be used to explore the effects of baseline characteristics on the primary endpoint. The association between the primary endpoint and cumulative sipuleucel-T product parameters (APC activation, APC count, and TNC count) will be assessed using logistic regression. The correlation between individual immune response

assays and cumulative sipuleucel-T product parameters will also be summarized. For Dendreon-sponsored studies in which data on OS are collected, the association of this endpoint and the individual immune response assays will be assessed using a Cox proportional hazards regression model.

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LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
ADT	androgen deprivation therapy
AE	adverse event
AOR	additional optional research
APC	antigen-presenting cell
CFR	Code of Federal Regulations
CI	confidence interval
CRF	case report form
CRPC	castration-resistant prostate cancer
CVE	cerebrovascular event
ECOG	Eastern Cooperative Oncology Group
ELISA	enzyme-linked immunosorbent assay
ELISPOT	enzyme-linked immunospot
FDA	Food and Drug Administration
GCP	good clinical practice
GM-CSF	granulocyte-macrophage colony-stimulating factor
HLA	human leukocyte antigen
HR	hazard ratio
ICF	informed consent form
ICH	International Conference on Harmonisation
IIT	investigator-initiated trial
IND	Investigational New Drug
INFγ	interferon-gamma
IRB	Institutional Review Board
IV	intravenous
LDH	lactate dehydrogenase
mCRPC	metastatic castration-resistant prostate cancer
PAP	prostatic acid phosphatase
PBMC	peripheral blood mononuclear cell
PSA	prostate-specific antigen
SAE	serious adverse event
TNC	total nucleated cell
US	United States

1.0 INTRODUCTION

1.1 Background

1.1.1 Prostate Cancer

Prostate cancer is the most common solid tumor malignancy in men in the United States (US). In 2013, it is estimated that there will be 238,590 new cases and 29,720 related deaths (American Cancer Society 2013). Approximately 80% of prostate cancer cases are diagnosed when the cancer is still confined to the primary site, and it is often treated with curative intent by radical prostatectomy, radiotherapy, brachytherapy, high intensity focused ultrasound, or cryotherapy. However, 20% to 40% of these subjects will eventually experience disease recurrence (Ward 2005), where an increased level of serum prostate-specific antigen (PSA) is evidence of biochemical failure and disease progression to advanced disease.

In men with recurrent disease, androgen deprivation therapy (ADT) is the current standard of care for androgen-dependent advanced prostate cancer and achieves temporary tumor control or regression in approximately 80% of subjects (Crawford 1989, Schellhammer 1997, Scher 1993). Unfortunately, virtually all patients who receive ADT will progress and their disease will spread to distant sites, most commonly bones and/or regional lymph nodes (Scher 1996, Small 1997). This castration-resistant state, known as castration-resistant prostate cancer (CRPC), is a non-curable and lethal disease. Management of metastatic CRPC (mCRPC) is a significant clinical challenge. Until recently, docetaxel was the only therapy to have demonstrated an improvement in overall survival (OS) in mCRPC patients (Petrylak 2004, Tannock 2004), and additional effective agents were warranted. Since 2010, five therapies have been approved for use in the US and have been shown to improve in OS in these patients (Heidegger 2013, Vapiwala 2013).

1.1.2 Sipuleucel-T

Provenge® (sipuleucel-T), an autologous cellular immunotherapy product designed to stimulate an immune response against prostate cancer, was approved in the US in 2010 for the treatment of men with asymptomatic or minimally symptomatic mCRPC. Sipuleucel-T consists of autologous peripheral blood mononuclear cells (PBMCs), including antigen-presenting cells (APCs), which have been activated during a defined culture period with a recombinant human protein. The recombinant human protein, PA2024, is composed of prostatic acid phosphatase (PAP), an antigen expressed in the majority of prostate adenocarcinomas, linked to granulocyte-macrophage colony-stimulating factor (GM-CSF), an immune cell activator (Goldstein 2002, Haines 1989). The processing of sipuleucel-T ex vivo has the potential benefit of achieving enhanced APC activation of subject cells due to removal from the immunosuppressive milieu of the subject, as suggested in preclinical models (Zou 2005).

1.1.2.1 Efficacy of Sipuleucel-T

A randomized, double-blind, controlled phase 3 trial (D9901, N=127 subjects) was conducted in men with asymptomatic mCRPC (Small 2006). Subjects randomized to sipuleucel-T had a 41% reduction in the risk of death relative to those randomized to a control product manufactured from autologous PBMCs without activation with PA2024 (hazard ratio (HR)=0.586 [95% confidence interval (CI): 0.388, 0.884] p=0.010, 2-sided log rank). The median OS was 25.9 months for subjects randomized to sipuleucel-T compared with 21.4 months for those randomized to control. In addition, subjects randomized to sipuleucel-T had a 31% reduction in the risk of disease progression (p=0.052, log rank). A second, smaller, randomized, double-blind, controlled phase 3 trial (D9902A, N=98 subjects) with the same design as D9901 demonstrated a 21% reduction in the risk of death for subjects randomized to sipuleucel-T, which did not reach statistical significance (HR=0.786 [95% CI: 0.484, 1.278]; p=0.331). However, the treatment effect was comparable to D9901 when the result was adjusted for key prognostic factors (Higano 2005). In the pivotal phase 3 D9902B (IMPACT) trial, 512 subjects with asymptomatic or minimally symptomatic mCRPC were randomized 2:1 to receive sipuleucel-T (N=341 subjects) versus control (N=171 subjects). Subjects who received sipuleucel-T had a 22.5% reduction in the risk of death relative to those subjects randomized to the control arm (HR=0.775; p=0.032; (Kantoff 2010)). The median OS in the sipuleucel-T arm was 25.8 months vs. 21.7 months in the control arm.

A combined, retrospective analysis of data from the IMPACT, D9901, and D9902A studies demonstrated that immune responses were correlated with efficacy in men with mCRPC who received sipuleucel-T. Cumulative APC activation, APC counts, and total nucleated cell (TNC) counts in sipuleucel-T correlated with OS ($p < 0.05$). The presence of antigen-specific immune responses in subjects was also correlated with OS ($p = 0.003$) (Sheikh 2013).

Sipuleucel-T has also been studied in men with androgen-dependent prostate cancer (Study P11; N = 176) (Beer 2011). While there was no statistically significant difference between control and sipuleucel-T on the primary endpoint of median time to biochemical failure (serum PSA $\geq$ 3.0 ng/mL), sipuleucel-T increased PSA doubling time (a strong predictor of prostate cancer mortality in this patient population (Albertsen 2004, D'Amico 2004, Freedland 2007, Roberts 2001, Sandler 2000, Valicenti 2006) following testosterone recovery compared with control (155 vs 105 days, $p = 0.038$).

1.1.2.2 Safety of Sipuleucel-T

More than 3,339 infusions of sipuleucel-T and control have been administered to men with prostate cancer in clinical trials. The most common adverse events (AEs) have been temporally related to APC product infusion. 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 Prescribing Information; (Dendreon 2011). Three of these studies were conducted in men with mCRPC (studies D9901, and D9902A, and D9902B [IMPACT]), and one study was conducted in men with androgen-dependent prostate cancer (Study P-11). In these randomized phase 3 studies, 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, and at a rate at least twice that of 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 Grade 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. CVE risk with sipuleucel-T treatment is being further evaluated in Study P10-3 (PROCEED), a registry of approximately 1,500 patients.

The sipuleucel-T Package Insert and Investigator's Brochure contain a review of clinical experience and product safety.

1.2 Study Rationale

Analysis of phase 3 trials of sipuleucel-T has demonstrated that OS is related to both product parameters (e.g., APC activation) and the subject's immune response to treatment-related antigens (PAP and PA2024) (Sheikh 2013). Castration-resistant prostate cancer is a heterogeneous disease, with varying symptoms and OS ranging from several months to several years (Scher 2011). The ability to accurately predict outcomes in men with CRPC is a crucial element in understanding response to treatment. While many studies have correlated clinical and laboratory variables with OS, 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 one at a time, and cannot assess the complex interactions 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 regard to control of CRPC.

This study will measure immune responses specific to PAP and PA2024 at multiple time points following sipuleucel-T treatment in subjects who are enrolled in a Dendreon-sponsored trial or registry, or an investigator-initiated trial [IIT], and receive sipuleucel-T. The goals are to describe the relationships between immune responses and prognostic factors, and to potentially identify biomarkers that are predictive of product parameters and immune responses. Additional optional research (AOR) will allow genomic analyses of DNA and gene expression analyses of

RNA in blood cells from those subjects who consent to the AOR. These analyses may identify a correlation between certain genomic or gene expression profiles and product parameters, immune responses, OS, or prognostic factors.

1.3 Study Conduct

The investigator will 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 Food and Drug Administration (FDA) Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. The investigator will follow all national, state, and local laws of the pertinent regulatory authorities.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

To evaluate the immune response induced by sipuleucel-T

2.2 Exploratory Objectives

- Where OS data are collected in the concurrent Dendreon-sponsored trial or registry, to evaluate the relationship between OS and immune response
- To explore the relationships between sipuleucel-T product parameters (APC activation, APC count, and TNC count) and immune response
- To explore relationships between OS and genomic or gene expression profiles

3.0 STUDY ENDPOINTS

3.1 Primary Endpoint

The percentage of subjects who exhibit any immune response at any post-treatment timepoint (6, 10, 14, 26, 39, and 52 weeks after the first infusion of sipuleucel-T) on the basis of:

- Interferon-gamma (IFNγ) enzyme-linked immunospot (ELISPOT) response to PAP or PA2024
- T cell proliferation response to PAP or PA2024
- Anti-PAP or anti-PA2024 humoral response

Antigen-specific T cell responses will be assessed using assays such as, but not limited to, H^3-thymidine uptake to measure the capacity of T cells to proliferate in response to antigen

stimulation, and IFNγ ELISPOT. The functional phenotypes of T cell subsets will be investigated using polychromatic flow cytometric analysis. Antigen-specific humoral responses will be measured using techniques such as enzyme-linked immunosorbent assay (ELISA).

3.2 Exploratory Endpoint

- Characterization of genomic or gene expression profiles

4.0 STUDY TREATMENT

All subjects who participate in this study will receive sipuleucel-T, and will potentially receive other medications as part of the trial in which they are concurrently enrolled; no additional study treatments will be required for this study. Each dose of sipuleucel-T is prepared using cells from a single leukapheresis procedure. A complete course of sipuleucel-T therapy consists of 3 doses of sipuleucel-T administered via intravenous (IV) infusion at approximately 2-week intervals. Please refer to the sipuleucel-T Package Insert or Investigator's Brochure for specific product information.

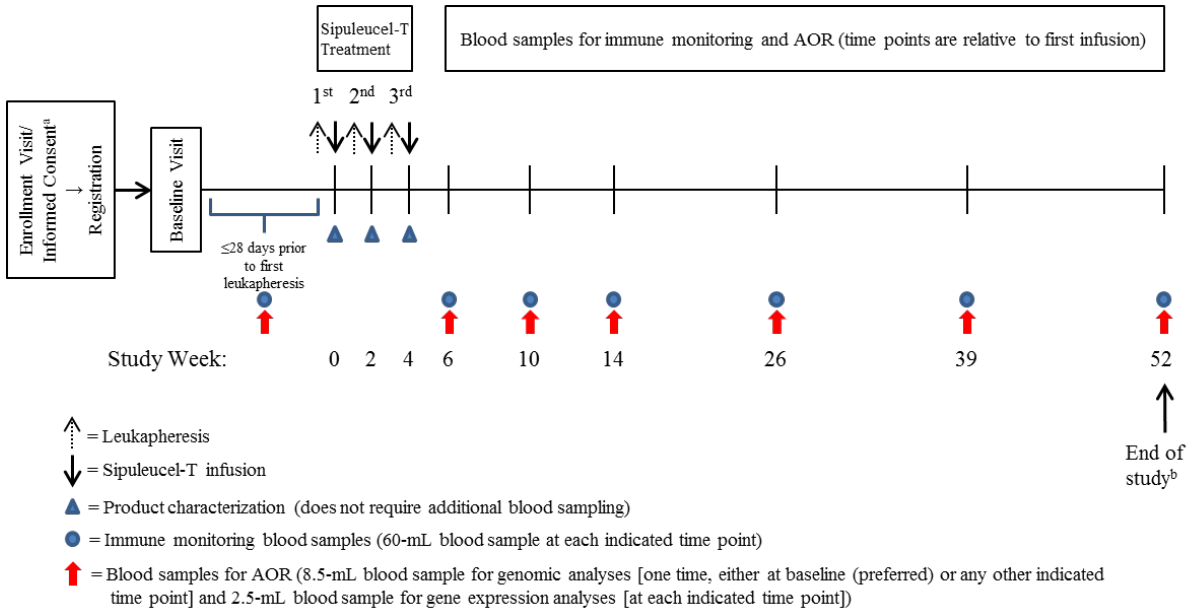
5.0 STUDY DESIGN AND CONDUCT

5.1 Study Design

This study (P11-4) is a multicenter trial in men ≥18 years of age with prostate cancer who are enrolled in a Dendreon-sponsored trial or registry, or an IIT, and will receive sipuleucel-T. Men who meet these criteria and have not yet undergone leukapheresis for their first dose of sipuleucel-T are eligible to participate in P11-4. Subject accrual and study duration for P11-4 will depend on the timing and population of the concurrent trials.

For P11-4, cellular and humoral immune responses will be assessed from 60-mL blood samples (immune monitoring blood samples; 5x10 mL heparin whole blood tubes and 1x10 mL serum tube) obtained at baseline (defined for the purposes of P11-4 sample collection as any time after informed consent, but prior to leukapheresis for the first dose of sipuleucel-T), as well as 6, 10, 14, 26, 39, and 52 weeks after the first infusion of sipuleucel-T (Figure 1; Appendix 1).

Figure 1: P11-4 Study Schematic



Abbreviation: AOR=additional optional research (blood samples for genomic and gene expression analyses, and other additional testing).

a Prior to consenting to participate in P11-4, subjects must have consented to participate in another Dendreon-sponsored trial or registry, or IIT, in which they will receive sipuleucel-T, and must sign the informed consent form for P11-4 **prior to the first scheduled leukapheresis procedure and any blood sampling for P11-4.**

b For each subject, participation in P11-4 may end prior to the collection of the week 52 immune monitoring and AOR blood samples if the subject withdraws from, or otherwise completes participation in, the concurrent trial.

As part of the normal manufacturing and quality control process, samples of cellular components from pre-culture and post-culture (sipuleucel-T) cells are used to confirm product quality attributes and potency (product characterization). Consent to participate in this study will allow unused portions of these pre- and post-culture samples, an additional 1% of the pre-culture cellular components, and immune monitoring blood samples to undergo additional analyses (e.g., flow cytometry or spectral analyses) to identify potential biomarkers of the immune response.

Subjects in this trial will be given the opportunity to consent to allow Dendreon to collect investigational blood samples for use in AOR, which will include both genomic and gene expression analyses, and other additional testing (e.g., human leukocyte antigen [HLA] phenotyping or protein array). Blood samples for AOR will be collected from only those subjects who agree to allow Dendreon to conduct these analyses, as described in Section 5.2.5.2.

Post-baseline blood sampling for immune monitoring and AOR will be performed only in subjects who receive at least 1 partial infusion (> 0 mL) of sipuleucel-T; subjects who do not receive at least 1 partial infusion of sipuleucel-T will no longer participate in this study.

Participation in this study will end following collection of the week 52 blood sample(s); when the subject no longer wishes to participate; or if the subject withdraws from, or otherwise completes participation in, the trial in which the subject is concurrently enrolled. After completion of this study (either through completion of all study visits or early withdrawal), subjects will continue to be followed for the trial in which they are concurrently enrolled.

5.2 Visit Procedures and Visit Windows

Please refer to the protocol for the trial in which subjects are concurrently enrolled for a full list of visit procedures. Procedures and visits required for P11-4 are listed below and presented in Figure 1 and Appendix 1. The permitted window for visits for P11-4 is ±1 week with the exception of baseline for the purposes of P11-4 sample collection, which occurs any time after informed consent for P11-4, but ≤ 28 days prior to leukapheresis for the first dose of sipuleucel-T.

5.2.1 Enrollment

Prior to consenting to enroll in P11-4, subjects must have consented to participate in a concurrent trial in which they may receive sipuleucel-T, and must sign the informed consent form (ICF) for P11-4 before any leukapheresis procedures are performed for preparation of sipuleucel-T, and before any blood samples for P11-4 are collected (Figure 1, Appendix 1). The process for obtaining informed consent for P11-4 is described in Section 9.4.

5.2.2 Registration

After signing the ICF for P11-4, subjects must be registered in the trial as outlined in the site reference manual.

5.2.3 Baseline Demographics and Disease Characteristics

Baseline for demographics and disease characteristics will be defined as the last known visit for the concurrent trial prior to leukapheresis for the first dose of sipuleucel-T.

For subjects concurrently enrolled in an IIT, baseline demographics and disease characteristics, including age/date of birth, height, weight, race, ethnicity, Eastern Cooperative Oncology Group (ECOG) Performance Status, Gleason score, prior prostate cancer treatment (yes/no), alkaline phosphatase, lactate dehydrogenase (LDH), serum PSA, hemoglobin, presence of visceral

metastases, number of bone metastases (0, 1-5, 6-10, or >10), and localization of disease (bone vs soft tissue) will be collected (Appendix 1).

Collection of baseline demographics and disease characteristics will not be required for P11-4 subjects who are concurrently enrolled in a Dendreon-sponsored trial or registry, as this information will be available in the database of the respective trial.

5.2.4 Sipuleucel-T Treatment

The date and lot number of each sipuleucel-T infusion will be recorded for subjects concurrently enrolled in an IIT (Appendix 1). Collection of sipuleucel-T infusion date and lot number will not be required for P11-4 subjects who are concurrently enrolled in a Dendreon-sponsored trial or registry, as this information will be available in the database of the respective trial or registry.

5.2.5 Immune Monitoring and Additional Optional Research

When providing consent to participate in this study, subjects will be given the option to consent to:

- Sampling for product characterization, immune monitoring, and other testing, with retention of samples by Dendreon or designee for up to 5 years, or
- Sampling for product characterization, immune monitoring, AOR, and other additional testing, with retention of samples by Dendreon or designee indefinitely.

5.2.5.1 Immune Monitoring

Blood samples for immune monitoring (60 mL) will be collected at baseline and 6, 10, 14, 26, 39, and 52 weeks after the first sipuleucel-T infusion (Figure 1, Appendix 1). If, for any reason, leukapheresis or sipuleucel-T infusion will occur on the same day as blood samples are to be drawn for immune monitoring, the immune monitoring sample will be obtained prior to leukapheresis or sipuleucel-T infusion.

5.2.5.2 Additional Optional Research

Subjects in this trial will be given the opportunity to consent to allow Dendreon to collect investigational blood samples for use in AOR, which will include both genomic and gene expression analyses, and other additional testing (e.g., human leukocyte antigen [HLA] phenotyping or protein array). Blood samples for AOR will be collected from only those subjects who agree to allow Dendreon to conduct these analyses.

For genomic analyses, an additional, 8.5 mL blood sample will be collected in a specialized tube containing an additive that stabilizes DNA (e.g., PAXgene® Blood DNA tube) one time only, either at baseline (preferred) or at any one of the other immune monitoring time points (6, 10, 14, 26, 39, or 52 weeks after the first infusion of sipuleucel-T). For gene expression analyses, an additional, 2.5 mL blood sample will be collected in a specialized tube containing an additive that stabilizes RNA (e.g., PAXgene Blood RNA tube) at all immune monitoring time points (baseline [any time after informed consent for P11-4, but ≤ 28 days prior to leukapheresis for the first dose of sipuleucel-T] and 6, 10, 14, 26, 39, and 52 weeks after the first infusion of sipuleucel-T). Gene expression analyses will be performed by Dendreon or designee.

If, for any reason, leukapheresis or sipuleucel-T infusion will occur on the same day as blood samples are to be drawn for AOR, the AOR samples will be obtained prior to leukapheresis or sipuleucel-T infusion.

5.3 Sample Retention

For subjects who consent to participate in P11-4, samples obtained for product characterization, immune monitoring, and other testing will be retained for up to 5 years following Dendreon's completion of this trial and then destroyed, except for subjects who provide additional consent for AOR.

For P11-4 subjects who provide additional consent for AOR, Dendreon or its designee may retain samples obtained for product characterization, immune monitoring, AOR, and other additional testing indefinitely.

Retained samples will be used for research only, will not be sold, and will not be identified using subject names or other personal identifiers.

Samples retained for immune monitoring or AOR may be sent to outside laboratories for testing. These samples will not be identified using patient names or other personal identifiers.

For subjects concurrently enrolled in a Dendreon-sponsored trial or registry, neither the subject nor the trial site will receive immune monitoring, AOR, or other test results. For subjects concurrently enrolled in an IIT, test results will be provided to the Principal Investigator or site for research purposes only and only as pre-specified in the approved IIT protocol. For these subjects, test results will not be released for clinical use, or for any use not specified in the approved IIT protocol.

6.0 SUBJECT SELECTION

6.1 Subject Eligibility

All men with prostate cancer aged ≥18 years who are enrolled in a Dendreon-sponsored trial or registry, or an IIT and will receive sipuleucel-T are eligible to participate in this trial if they have not yet undergone leukapheresis for their first dose of sipuleucel-T.

6.2 Removal of Subjects from Assessment

Whenever possible, subjects should remain on study. The investigator may withdraw a subject from assessment if, in his or her clinical judgment, it is in the best interests of the subject.

Subjects may discontinue their participation in the trial at any time without prejudice, and without affecting eligibility for the trial in which they are concurrently enrolled.

Participation in this study may end prior to the collection of the week 52 blood sample(s), if the subject withdraws from, or otherwise completes participation in, the concurrent trial.

At the time of withdrawal from the trial, subjects have the right to request that any samples not yet analyzed be destroyed.

7.0 STATISTICAL CONSIDERATIONS

7.1 Methods

7.1.1 Immune Response Variables

The immune response will be assessed with the following assays:

• T cell IFN-γ ELISPOT response to PA2024 and PAP

• T cell proliferation response to PA2024 and PAP by H^3-thymidine uptake

• Humoral response to PA2024 and PAP by ELISA

A subject will be declared a responder for a particular assay if the observed result is greater than a threshold value, where the threshold value is determined from all responses measured at baseline that ensures a sufficiently low false positive rate (i.e., 5% or less).

7.2 Statistical Analysis

7.2.1 Primary Analysis

The primary endpoint is the percentage of subjects who exhibit animmune response at any post-treatment time point (6, 10, 14, 26, 39, and 52 weeks after the first infusion of sipuleucel-T). The primary immune response analysis population will include all subjects who receive all 3 infusions of sipuleucel-T; summaries will also be generated for the population of patients who receive at least one partial infusion of sipuleucel-T. Logistic regression will be used to explore the effect of baseline characteristics on the primary endpoint. Repeated measurement mixed models will be used to explore the individual immune response assays as continuous endpoints over time. Transformation of the continuous outcome may be applied if the original data are not normally distributed. Key subgroups of interest will be defined on the basis of baseline demographics and disease characteristics (e.g., age, race, ECOG status, and serum PSA).

Table 1 summarizes the minimum detectable percent difference in immune responders with 90% power using a two independent proportions test at the two-sided 0.05-level between two subgroups, with the smaller subgroup representing 10% of total sample size and a minimum immune response incidence in each subgroup of 20% to 80%. In the IMPACT study, 79% of sipuleucel-T subjects had an immune response by any of the 3 assays to either PA2024 or PAP at any time point post-baseline (Sheikh 2013).

Table 1: Minimal Detectable Percentage of Immune Responders by Sample Size

Total Sample Size	Sample Size per Subgroup	Immune Responders (Smallest % in Either Subgroup)	Minimum Detectable Difference (%)
1000	900/100	20%	15%
1000	900/100	50%	17%
1000	900/100	80%	12%
500	450/50	20%	22%
500	450/50	50%	23%
500	450/50	80%	16%
200	180/20	20%	36%
200	180/20	50%	35%
200	180/20	80%	20%

7.2.2 Exploratory Analyses

For subjects concurrently enrolled in Dendreon-sponsored trials in which OS data are collected, the association of this endpoint and the individual immune response assays will be assessed using a Cox proportional hazards regression model. Key subgroups of interest will be defined on the basis of baseline demographics and disease characteristics (e.g., age, race, ECOG status, and serum PSA). Similar analyses may be conducted should sufficient data for other clinical endpoints be available from the trial(s) in which subjects are concurrently enrolled.

The association between immune response and sipuleucel-T product parameters (APC activation, APC count, and TNC count) will be assessed using logistic regression. The correlation between individual immune response assays and cumulative sipuleucel-T product parameters will also be summarized.

The relationship between gene expression profile at various time points and OS will be assessed using Cox proportional hazards regression models.

Repeated measurement mixed models will be used to explore genomic parameters and the profile of gene expression parameters over time to potentially provide insights into the immune response as it relates to the mechanism of action of sipuleucel-T. Transformation of the gene expression parameters may be applied if the original data are not normally distributed. Groupings of genes (e.g., 2-gene models) will also be explored.

8.0 REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS

Reporting requirements for serious adverse events (SAEs) are described in the respective protocol for the trial in which each subject is concurrently enrolled.

9.0 REGULATORY REQUIREMENTS

9.1 Required Documentation

Dendreon must receive the following P11-4 documentation prior to initiation of the study:

- Regulatory documents required by the trial in which the subject is concurrently enrolled
- Signed protocol signature page
- Signed Form FDA 1572
- Curriculum vitae of the Principal Investigator, updated within the past 2 years
- Copies of current medical licenses for the Principal Investigator and all sub-investigators

- Financial disclosure forms for the Principal Investigator and all sub-investigators
- Copy of Institutional Review Board (IRB) approval letter for 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 be responsible for ensuring that all site personnel conduct the study in compliance with the Declaration of Helsinki and the ICH E6 Guideline for GCP, including the archiving of essential documents. The Principal Investigator will also ensure adherence to all national, state, and local laws of the pertinent regulatory authorities, including Federal regulations / guidelines set forth in 21 Code of Federal Regulations (CFR) § 11, 50, 54, 56, and 312.

The Principal Investigator will be responsible for the subject's compliance with the protocol, and may meet periodically with the Dendreon study monitor or Dendreon designee.

All investigators must complete and return financial disclosure statements (including information on spouses, legal partners, or dependent children) before study initiation. The 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). The investigators must promptly verify this information by completing and returning financial disclosure statements every 2 years throughout the study regardless of whether or not any information has changed.

In addition, the Principal Investigator is responsible for providing Dendreon an adequate final report shortly after he/she completes participation in the study, in accordance with 21 CFR § 312.64.

9.3 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. Subject's 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 are to be available for inspection on request by the FDA, Dendreon's representative, or the IRB. Dendreon may retain in its files copies of subject medical information required for auditing of case report forms (CRFs).

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

9.4 Informed Consent

The investigator must ensure that each subject understands how the study will be conducted, and how he will participate if he so chooses. 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 arise. The subject shall be given sufficient time to properly consider the information and to make an informed decision regarding consent. When all questions have been answered and the investigator or delegate is assured that the subject understands the implications of study participation, the subject will be asked to provide written consent to participate in the study by signing the ICF. The investigator or delegate will document in the subject's medical chart or progress notes that the written informed consent process occurred, including that consent was obtained prior to the initiation of study-related procedures, and will provide a copy of the signed ICF to the subject. Eligibility for the trial in which subjects are concurrently enrolled will not be affected by refusal to participate in P11-4.

The ICF, including any amendments, must be reviewed and approved by the designated IRB and by Dendreon staff or its designee. Subjects must have consented to participate in another Dendreon-sponsored trial or registry, or IIT, prior to consenting to participate in P11-4, and must sign the ICF for P11-4 prior to their first scheduled leukapheresis procedure and any blood sampling for this trial.

If an amendment to the protocol changes the subject participation schedule in scope or activity, or increases the potential risk to the subject, the ICF will be revised and submitted to the IRB for review and approval. The revised ICF should be used to obtain written consent from a subject currently participating in the study if the information is pertinent to him 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.

The subject's medical record should contain written documentation indicating that informed consent was obtained prior to study enrollment.

9.5 Institutional Review Board

The Principal Investigator is responsible for ensuring that this protocol and relevant supporting data are submitted to the appropriate IRB for review and approval before the study can be initiated. Dendreon or its designee 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 Principal 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 Principal Investigator when the study is complete. The Principal Investigator is responsible for notifying the relevant IRB of any serious adverse event (SAE) which occurs in a subject who is participating at their site, and of any Investigational New Drug (IND) Safety Reports issued by Dendreon, per IRB policy.

10.0 PROTOCOL MANAGEMENT AND ADMINISTRATIVE CONSIDERATIONS

10.1 Study Documentation

The Principal Investigator and study personnel are responsible for maintaining a 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:

- Subject files, containing the completed CRFs, supporting source documentation from the medical record, and the signed ICFs.
- Regulatory files, containing the protocol with all amendments and protocol signature pages, copies of all other essential regulatory documentation, and all correspondence between the trial site, the IRB, and Dendreon.

Records are to be available for at least 5 years after study completion and the FDA is so notified.

10.2 Data Collection

Trained study personnel will be responsible for entering data on the observations, tests, and assessments specified in the protocol according to the CRF Instructions. Data from the CRF will be entered into a central database and any changes will be tracked to provide an audit trail. At the completion of the study, a copy of the final clinical study report will be submitted to the FDA.

10.3 Protocol Interpretation and Compliance

To ensure accurate interpretation and implementation of the study, the procedures and endpoints defined in the protocol will be carefully reviewed by the Investigator and his or her staff prior to the time of study initiation.

10.4 Study Monitoring

A representative from Dendreon may visit the study site periodically to monitor adherence to the protocol, adherence to applicable FDA regulations, and the maintenance of adequate and accurate clinical records. CRFs will be reviewed to ensure that sample collection information is

recorded as specified by the protocol. The Dendreon representative will be permitted to access subject's complete medical records and other source documentation as needed to appropriately monitor the study.

10.5 Disclosure of Data and Publication

The Principal Investigator or anyone else 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, the Principal Investigator or anyone else working on the study may not include any confidential information in any such publication or disclosure.

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APPENDIX 1: P11-4 SCHEDULE OF ASSESSMENTS

Visit	Baseline[a]	Immune Monitoring and AOR (6, 10, 14, 26, 39, and 52 weeks ± 1 week after the first infusion)
Informed Consent	X[b]	
Enrollment	X	
Registration	X	
Baseline Demographics		
Age / Date of Birth	X[c]	
Height	X[c]	
Weight	X[c]	
Race and ethnicity	X[c]	
Baseline Disease Characteristics		
ECOG Performance Status	X[c]	
Gleason Score	X[c]	
Prior Prostate Cancer Treatment (yes/no)	X[c]	
Alkaline phosphatase, LDH, and serum PSA	X[c]	
Hemoglobin	X[c]	
Presence of Visceral Metastases	X[c]	
Number of Bone Metastases (0, 1-5, 6-10, > 10)	X[c]	
Localization of Disease (bone vs. soft tissue)	X[c]	
Sipuleucel-T Treatment Monitoring	X[d]	
Immune Monitoring Blood Sample (60 mL: 5x10 mL heparin whole blood; 1x10 mL serum)	X	X
AOR Blood Sample[e]	X	X

Abbreviations: AOR=additional optional research (for genomic and gene expression analyses, and other additional testing); ICF=informed consent form; IIT=investigator-initiated trial; LDH=lactate dehydrogenase; PSA=prostate-specific antigen.

a Baseline is defined for the purposes of P11-4 sample collection as any time after informed consent, but prior to leukapheresis for the first dose of sipuleucel-T.

b Subjects must have provided informed consent to participate in a Dendreon-sponsored trial or registry, or IIT, prior to consenting to participate in P11-4, and must sign the ICF for P11-4 **prior to the first scheduled leukapheresis procedure, and any blood sampling for P11-4**.

c Only for subjects concurrently enrolled in an IIT.

d Record date and lot number of each sipuleucel-T infusion for subjects concurrently enrolled in an IIT.

e For those subjects who consent to AOR only. For genomic analyses, an additional, 8.5-mL blood sample will be collected in a specialized tube (e.g., PAXgene® Blood DNA tube) one time, either at baseline (preferred) or an immune monitoring and AOR visit. For gene expression analyses, an additional, 2.5-mL blood sample will be collected in a specialized tube (e.g., PAXgene Blood RNA tube) at baseline and all immune monitoring and AOR visits.