A RANDOMIZED PHASE 3, OPEN-LABEL TRIAL OF SIPULEUCEL-T ADMINISTERED TO PATIENTS ON ACTIVE SURVEILLANCE FOR NEWLY DIAGNOSED PROSTATE CANCER

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INVESTIGATIONAL PRODUCT:	Sipuleucel-T
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PRINCIPAL INVESTIGATOR PROTOCOL SIGNATURE PAGE

A Randomized Phase 3, Open-label Trial of Sipuleucel-T Administered to Patients on Active Surveillance for Newly Diagnosed Prostate Cancer

Amendment 2: 25 January 2019

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

Principal Investigator Name:

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Title:

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Address:

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Facsimile:

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Signature:

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Date:

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PROTOCOL SYNOPSIS

Protocol Title: A Randomized Phase 3, Open-Label Trial of Sipuleucel-T Administered to Patients on Active Surveillance for Newly Diagnosed Prostate Cancer

Protocol Number: P17-1

Clinical Phase: 3

Investigational Product, Dosage Form, Route, and Dose Regimen:

Sipuleucel-T is an autologous cellular immunotherapy available as a suspension for intravenous infusion. Sipuleucel-T consists of autologous peripheral blood mononuclear cells (PBMC), including antigen presenting cells (APCs) that have been activated during a defined culture period with a recombinant human protein, PAP-GM-CSF, consisting of prostatic acid phosphatase (PAP), an antigen expressed in prostate cancer tissue, linked to granulocyte-macrophage colony-stimulating factor (GM-CSF), an immune cell activator. Each dose of sipuleucel-T contains a minimum of 50 million autologous CD54+ cells activated with PAP-GM-CSF, suspended in 250 mL of Lactated Ringer's Injection, USP.

The active components of sipuleucel-T are autologous APCs and PAP-GM-CSF. During culture, the recombinant antigen binds to and is processed by APCs into smaller protein fragments. The recombinant antigen is designed to target APCs, and may help direct the immune response to PAP. Minimal residual levels of the intact PAP-GM-CSF are detectable in the final sipuleucel-T product.

The patient's PBMCs are obtained via a standard leukapheresis procedure approximately 3 days prior to the infusion date. Due to the autologous nature of sipuleucel-T, it is important that the patient and physician adhere to the personalized leukapheresis and infusion schedules.

The cellular composition of sipuleucel-T is dependent on the composition of cells obtained from the patient's leukapheresis. In addition to APCs, the final product contains T cells, B cells, natural killer (NK) cells, and other cells. The number of cells present and the cellular composition of each sipuleucel-T dose will vary.

The potency of sipuleucel-T is in part determined by measuring the increased expression of the CD54 molecule, also known as ICAM-1, on the surface of APCs after culture with PAP-GM-CSF. CD54 is a cell surface molecule that plays a role in the immunologic interactions between APCs and T cells, and is considered a marker of immune cell activation.

In-process and final sterility tests are initiated prior to shipping, but the final results are not available for up to 7 days. Sipuleucel-T is released for shipping based on acceptable results from 2-day incubation of the in-process sterility test (Sipuleucel-T, 2017).

Reference Product, Dosage Form, Route, and Dose Regimen:

No reference product will be used in this clinical study.

Primary Objective:

- To assess the efficacy of sipuleucel-T in reducing histopathologic reclassification to a higher Gleason grade in prostate cancer subjects on active surveillance (AS)

Secondary Objectives:

- To assess the differential receipt of local or systemic therapy (surgery, radiation, androgen deprivation therapy (ADT)) in each study arm, and the reasons for receipt of further local or systemic therapy
- To assess differences in quality of life (i.e., patient-reported outcomes (PRO)) between sipuleucel-T and control arms
- To evaluate the safety of sipuleucel-T in men with low to intermediate risk localized prostate cancer

Exploratory Objectives:

- To evaluate in the sipuleucel-T arm the association of peripheral blood and tumor microenvironment immunologic responses with reclassification of Gleason grade over time
- To evaluate clinical assessments and potential correlation to sipuleucel-T
- To evaluate prostate tissue genomics

Primary Endpoint:

- Proportion of subjects without histological reclassification (Gleason group upgrade) within 36 months of randomization as determined by Blinded Independent Central Review (BICR)
    - Upgrade is defined as subjects at randomization with either International Society of Urological Pathology (ISUP) Grade Group 1 (Gleason 3+3) upgraded to Grade Group 2 (Gleason 3+4) or higher or subjects at randomization with Grade Group 2 upgraded to Grade Group 3 (Gleason 4+3) or higher.

Secondary Endpoints:

- To determine the number of subjects with subsequent prostate cancer treatment (e.g., surgery, radiation, ADT) in each study arm

- Characterization of PROs by Memorial Anxiety Scale for Prostate Cancer (MAX-PC), Short Form 12 Health Survey (SF-12), The Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP), International Prostate Symptom Score (IPSS) at baseline and 12-, 24-, and 36-month visits after randomization

- To evaluate safety by determining the incidence of adverse events (AEs), assessing laboratory data for clinically significant laboratory abnormalities and evaluating physical examination (PE) findings in each study arm

Exploratory Endpoints:

- To calculate the correlation of prostate tissue and peripheral immune responses, as well as product parameters to sipuleucel-T efficacy

- To determine, in the cohort of subjects having a radical prostatectomy, the number of subjects with an ISUP Grade Group change (up- or down-grade) determined by BICR from radical prostatectomy tissue histology in each study arm

- To measure the percentage of subjects with a negative biopsy at any post-randomization biopsy assessment in each study arm

- To compare the proportion of subjects with clinical risk group progression (e.g., Cancer of the Prostate Risk Assessment (CAPRA) and National Comprehensive Cancer Network (NCCN) prostate cancer risk groups) between study arms

- To calculate Prostate-specific antigen (PSA) velocity from randomization through study completion in each study arm

- To determine the association of prostate cancer tissue genomic profile and sipuleucel-T treatment

Study Design and Duration:

This is a multicenter, randomized, open-label study of immunotherapy with sipuleucel-T compared to control subjects followed on AS. The study will enroll subjects being followed by AS and initially diagnosed within 12 months prior to Screening with either ISUP Grade Group 1 or 2 adenocarcinoma of the prostate.

This study consists of 3 phases (see Table 1 and Table 2):

Screening Phase:

The Screening Phase will begin at the completion of the informed consent process and continues until randomization. Screening procedures will be performed up to 30 days prior to randomization.

The following assessments will be performed on all subjects during the Screening Phase:

- BICR of prostate biopsy slides obtained from local pathologist (ISUP Grade Group and Gleason Score)
- Clinical evaluations (demographics, medical history, PE & vital signs, digital rectal examination (DRE), Eastern Cooperative Oncology Group (ECOG) performance status, cardiovascular risk assessment & electrocardiogram (ECG))
- Cardiovascular and thrombosis disease history
- Concomitant medications
- All anti-prostate cancer therapies
- PROs/Quality of life questionnaires
- Virology serology (HBsAg, HBsAb, HBcAb, HCV antibody (Ab), if Ab positive (Ab+) then HCV RNA), HIV-1, HIV-2 antibody screen and HTLV-1, HTLV-2 antibodies
- Hematology and chemistry
- PSA
- Total testosterone

Active Phase:

The Active Phase will begin at randomization and continues through completion of the end of Active Phase study visit (within 30 days of Biopsy 2) or until the study is terminated by the sponsor.

Subjects who withdraw consent and discontinue from the study prior to completing the end of Active Phase study visit will undergo an Early Withdrawal visit within 30 days following discontinuation notice. Subjects are encouraged to have, a s standard of care, a systematic prostate biopsy (≥10 cores) with or without MRI at the investigator's discretion prior to study withdrawal. The H&E and special-stained slides from this biopsy will be submitted for BICR determination of their ISUP Grade Group classification prior to study withdrawal.

After Screening assessments are completed, eligible subjects will be randomized 2:1 to the sipuleucel-T arm or the control arm. Subjects randomized to sipuleucel-T arm will undergo their first leukapheresis within 60 days of randomization and will receive 3 infusions of sipuleucel-T at approximately 2-week intervals. Subjects randomized to the control arm will be followed on AS as described in the schedule of events (Table 2).

Subjects randomized to the sipuleucel-T arm will be evaluated at 0, 2, 4, 6, 10, 14, and 26 weeks following the first infusion for:

- Immune responses (Week 0 prior to first infusion is baseline)
- All anti-prostate cancer therapies
- Concomitant medications
- AEs and serious adverse events (SAEs) (per reporting requirements for the sipuleucel-T arm)

Subjects randomized to the control arm will be evaluated (office visit or phone) at 3 months following randomization for:

- Survival status
- All anti-prostate cancer therapies
- Concomitant medications
- All AEs and SAEs

Subsequently, all subjects in the sipuleucel-T and control arms will be followed every 6 months from date of randomization for at least 36 months for:

- Immune responses (sipuleucel-T arm only)
- Survival status
- PSA levels (should be collected prior to DRE and biopsy procedures)
- DRE assessments
- Prostate cancer disease progression
- All anti-prostate cancer therapies
- Concomitant medications
- All AEs and SAEs

Note, for subjects randomized to the sipuleucel-T arm, scheduled events for the 26-week visit post first infusion and first 6-month visit post-randomization may take place on the same visit and only one set of immune samples need to be collected

During the Active Phase, all subjects in the sipuleucel-T and control arms will complete:

- PROs/Quality of life questionnaires (Max-PC, SF-12, EPIC-CP, and IPSS) annually (12-, 24-, and 36-month visits) post randomization. PROs/Quality of life questionnaires should be collected prior to any procedures on these specified visits.

- Two (2) systematic biopsies (Biopsy 1 & Biopsy 2; ≥10 cores each) will be administered as standard of care. Additional cores may be collected by MRI guidance per investigator discretion; however, MRI targeted cores collected at baseline should be repeated for Biopsy 1 & Biopsy 2 (Appendix 7).

Biopsy 1 will be administered between 12 and 18 months, and Biopsy 2 will be administered between 33 and 39 months post randomization. All hematoxylin and eosin (H&E) and special stained slides will be assessed for histopathologic grading by BICR. Slides from each biopsy will be considered as a group to determine the ISUP Grade Group as opposed to any single slide. The BICR is blinded to a subject's study arm randomization. BICR will receive the local pathology staining methods and Gleason score. All subject information should be redacted from the local pathology reports and slides. Local pathology reports and slides will be identified only by study subject number. All slides will be returned to the clinical trial site.

Post randomization, central pathology requested formalin-fixed paraffin-embedded (FFPE) tissue blocks identified by study subject number will be sent to the central pathology lab for cutting and slide preparation for immunohistochemistry (IHC) and genomic analysis. All tissue blocks will be returned to the clinical trial site.

Upon study completion, if the primary endpoint is met subjects on the control arm may be offered sipuleucel-T.

Follow-up Phase:

Once a subject from either the sipuleucel-T or control arms completes the end of Active Phase visit, they will enter the Follow-up Phase and complete Follow-up Phase visits every 6 months starting from their last Active Phase visit. The Follow-up Phase visits end when the last subject enrolled completes Biopsy 2 and end of Active Phase visit or until the study is terminated by the sponsor. All subjects will be assessed for:

- Survival status

- PROs/Quality of life questionnaires

- PSA levels (as available by local laboratory)

- Prostate cancer disease progression

- All anti-prostate cancer therapies

- All AEs and SAEs

AE and SAE Reporting Requirements:

All AEs and SAEs in the sipuleucel-T arm and control arm will be collected from randomization through the subject's last study visit. AEs and SAEs will be reported and recorded in the subject's medical record and entered on their eCRF. All SAEs will also be reported on sponsor's SAE Report Form.

All AEs and SAEs reported in either the sipuleucel-T or control arms will be followed by the investigator until resolution, return to baseline, or the investigator determines that no further improvement is expected until study completion. The start and stop dates, description, seriousness, toxicity, relationship to study treatment, and outcome will be recorded.

SAEs must be reported to sponsor or designee within 24 hours of the clinical trial site's awareness of the events by completing the sponsor's SAE Report Form. If access to the SAE Report Form is unavailable for any reason, the SAE information must be reported to sponsor or designee within 24 hours by email or facsimile and a completed written report using sponsor's SAE Report form within 3 business days to:

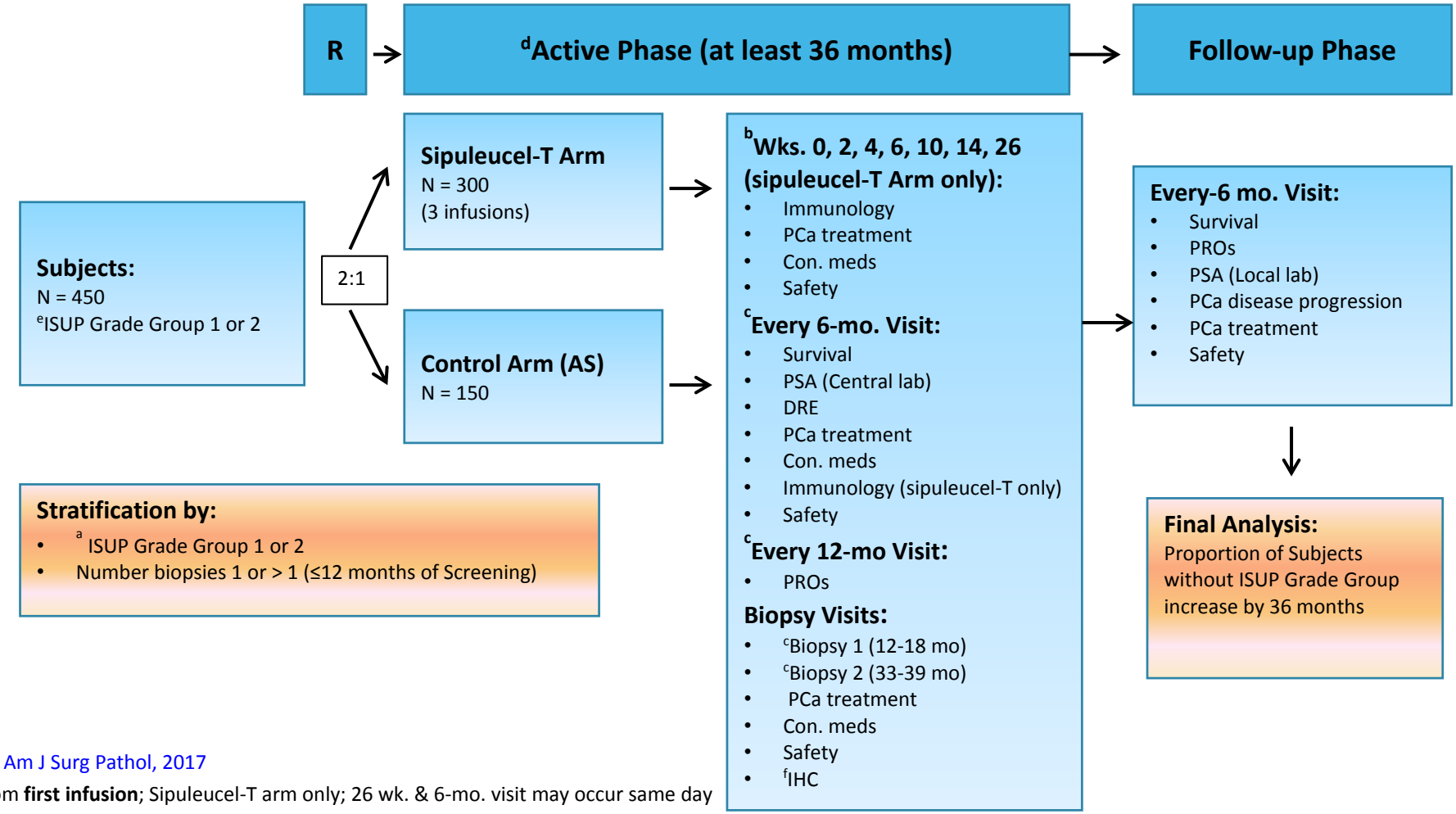
Dendreon Pharmaceuticals LLC

Attention: DrugSafety@dendreon.com

Significant new information regarding each SAE must be reported to sponsor or designee by recording the information on the SAE Report Form within 24 hours of the clinical trial site's awareness of the new information and reported as noted above.

The figure below presents a schematic of the study design.

Figure 1: Study Schematic



[a]Epstein JI, Am J Surg Pathol, 2017

[b]Weeks from **first infusion**; Sipuleucel-T arm only; 26 wk. & 6-mo. visit may occur same day

[c]Months from **randomization in both arms**

[d] Active Phase ends when the last subject enrolled completes 36-mo. Biopsy and end of Active Phase visit

[e]International Society Urological Pathology (ISUP); Grade Group 1 = Gleason 3+3; Grade Group 2 = Gleason 3+4

[f]Immunohistochemistry (IHC)

Table 1: Schedule of Events for Subjects Randomized to Sipuleucel-T

Item	Screening /Baseline[a]	Randomization[b]	Leukapheresis 1	Infusion 1 (Week 0)	Leukapheresis 2	Infusion 2	Leukapheresis 3	Infusion 3	Weeks 2, 4, 6, 10, 14, 26 IM Visits Post 1st Infusion[e]	Every 6-Month Visit Post Randomization[e]	Every 12-mont Visit	Biopsy 1 & Biopsy 2	End of Active Phase Visit [n]	End of Active Phase and Beginning of Follow up Phase[o]	Every 6-Month Follow Up Visit[o]	Early Withdrawal Visit [p]
Visit Window	≤30 days prior randomization			~3 days after leukapheresis 1		~3 days after leukapheresis 2		~3 days after leukapheresis 3	± 7 days	± 14 days	± 14 days	12 to 18 & 33 to 39 months post randomization	Within 1 mo. of Biopsy 2		± 1 Month	
Informed Consent	X															
Prostate Biopsy	X[c]											X[j]				
Leukapheresis			X[s]		X		X									
Sipuleucel-T Infusion				X		X		X								
Clinical Evaluations																
Demographics	X															
Medical History	X															
Physical Examination and Vital Signs[d]	X		X		X		X						X			X
Digital Rectal Exam	X									X						
ECOG Performance Status	X															
Cardiovascular Risk Factors[q]	X															
ECG	X															
AEs and SAEs			X	X	X	X	X	X	X	X		X	X		X	X
Concomitant Medications	X		X	X	X	X	X	X	X	X		X	X			X
Prostate Cancer Treatment[h]	X		X	X	X	X	X	X	X	X		X	X		X	X
Patient Reported Outcomes[i]	X										X				X	X
Survival Status[f]										X		X	X		X	X

Item	Screening /Baseline[a]	Randomization[b]	Leukapheresis 1	Infusion 1 (Week 0)	Leukapheresis 2	Infusion 2	Leukapheresis 3	Infusion 3	Weeks 2, 4, 6, 10, 14, 26 IM Visits Post 1'st Infusion[e]	Every 6-Month Visit Post Randomization[e]	Every 12-mont Visit	Biopsy 1 & Biopsy 2	End of Active Phase Visit [n]	End of Active Phase and Beginning of Follow up Phase[o]	Every 6-Month Follow Up Visit[o]	Early Withdrawal Visit [p]
Visit Window	≤30 days prior randomization			~3 days after leukapheresis 1		~3 days after leukapheresis 2		~3 days after leukapheresis 3	± 7 days	± 14 days	± 14 days	12 to 18 & 33 to 39 months post randomization	Within 1 mo. of Biopsy 2		± 1 Month	
Laboratory Tests																
IHC and Gleason Score	X[c]											X[j]				
Viral Serology[m]	X															
Chemistry and Hematology [r]	X												X			X
PSA	X[g]									X[g]					X[t]	X
Total Testosterone	X															
Immune Monitoring Sample Collection																
100 mL sample [l]				X[k]					X[k]	X						
8.5 mL sample PAXGENE RNA				X[k]					X[k]	X						
2.0 mL sample PAXGENE DNA				X[k]												

[a] All screening/baseline procedures must occur within 30 calendar days prior to randomization, with the exception of written informed consent and diagnostic biopsy.
[b] Randomization is the final event of Screening once eligibility of subject is confirmed by the PI.
[c] Pre-study biopsy(ies) is (are) not a study procedure and the first diagnosed biopsy must have been performed ≤12 months of signing ICF. The biopsy (ies) H&E and special stained slides that were used for prostate cancer diagnosis must be submitted for BICR to determine subject eligibility.
[d] Complete PE including vital signs done at the clinical site at Screening (genitourinary, skin, pulmonary, cardiovascular, neurological, gastrointestinal & musculoskeletal) and abbreviated PE per PI's discretion within 7 days prior to each leukapheresis and End of Active Phase Visit. Weight will be measured at each PE; height will be measured at Screening only.
[e] The 26-week post-first-infusion visit and first 6-month visit post randomization may occur on the same visit day and only one set of immune samples need to be collected if the visits fall on the same day.
[f] Survival status will not be obtained for subjects that are lost to follow up or withdrawn from the study.
[g] PSA should be collected prior to DRE and biopsy procedures.
[h] Any prostate cancer treatment (e.g., surgery, radiation, androgen deprivation therapy).
[i] Patient reported outcomes/Quality of life questionnaire (IPSS, Max-PC, SF-12 and EPIC-CP) should be collected every 12 months (12-, 24-, and 36-month visits) prior to any procedures.
[j] Biopsy 1 may take place between 12 months and 18 months post randomization. Biopsy 2 may take place between 33 months and 39 months post randomization.
[k] Immune monitoring sample collection time points are calculated from the date of first infusion (note: not from randomization). Samples collected on infusion days (i.e., Weeks 0, 2, 4) will be drawn prior to starting the sipuleucel-T infusion. A single PAXGENE DNA sample is only collected at Week 0.
[l] Blood draws for immune response analyses: 100mL total draw (90ml into NaHeparin Vacutainer for PBMC isolation and 10mL into no-anticoagulant vacutainer tubes for serum isolation).
[m] Viral serology consists of hepatitis panel (HBsAg, HBsAb, HBcAb, HCV antibody(Ab), if Ab+ then HCV RNA)), HIV-1, HIV-2 antibody screen, and HTLV-1, HTLV-2 antibodies
[n] End-of-Active Phase visit will take place within 30 days following Biopsy 2.
[o] Follow-up visits will start 6 months after the End-of-Active Phase visit.
[p] The early withdrawal visit must occur within 30 days of the last visit.
[q] Risk factors for cardiovascular events will include diabetes mellitus, smoking history, family history, left ventricular hypertrophy, atrial fibrillation, hypertension, myocardial infarction and other cardiovascular disease.
[r] Chemistry and/or hematology should be completed at a local lab within 7 days of leukapheresis as requested by the Apheresis center
[s] First leukapheresis will be given within 60 days of randomization
[t] PSA collected per standard of care, analyzed by local lab

Table 2: Schedule of Events for Subjects Randomized to Control

Item	Screening /Baseline[a]	Randomization[b]	3-Month Visit Post Randomization[o]	Every 6-Month Visit Post Randomization	Every 12-mont Visit	Biopsy 1 & Biopsy 2	End of Active Phase Visit[k]	End of Active Phase and Beginning of Follow up Phase[l]	Every 6-Month Follow Up Visit[l]	Early Withdrawal Visit[m]
Visit Window	≤30 days prior randomization		± 14 days	± 14 days	± 14 days	12 to 18 & 33 to 39 months post randomization	Within 1 mo. of Biopsy 2		± 1 Month	
Informed Consent	X									
Prostate Biopsy	X[c]					X[i]				
Clinical Evaluations										
Demographics	X									
Medical History	X									
Physical Examination and Vital Signs[d]	X						X			X
Digital Rectal Exam	X			X						
ECOG Performance Status	X									
Cardiovascular Risk Factors[n]	X									
ECG	X									
AEs and SAEs			X	X		X	X		X	X
Concomitant Medications	X		X	X		X	X			X
Prostate Cancer Treatment[g]	X		X	X		X	X		X	X
Patient Reported Outcomes[h]	X				X				X	X
Survival Status[e]			X	X		X	X		X	X
Laboratory Tests										
IHC and Gleason Score	X[c]					X[i]				
Viral Serology[j]	X									
Chemistry and Hematology	X						X			X
PSA	X[f]			X[f]					X[p]	X
Total Testosterone	X									

[a] All screening/baseline procedures must occur within 30 calendar days prior to randomization, with the exception of written informed consent and diagnostic biopsy

[b] Randomization is the final event of Screening once eligibility of subject is confirmed by the PI.

[c] Pre-study biopsy(ies) is (are) not a study procedure and must have been performed ≤12 months of signing ICF. The biopsy (ies) H&E and special stained slides that were used for prostate cancer diagnosis must be submitted for BICR to determine subject eligibility.

[d] Complete PE including vital signs done at the clinical site at Screening (genitourinary, skin, pulmonary, cardiovascular, neurological, gastrointestinal & musculoskeletal) and abbreviated PE per PI's discretion at the End of Active Phase Visit. Weight will be measured at each PE; height will be measured at Screening only.

[e] Survival status will not be obtained for subjects that are lost to follow up or withdrawn from the study.

[f] PSA should be collected prior to DRE and biopsy procedures

[g] Any prostate cancer treatment (e.g., surgery, radiation, androgen deprivation therapy)

[h] Patient reported outcomes/Quality of life questionnaire (Max-PC, SF-12 EPIC-CP, and IPSS) should be collected every 12 months (12-, 24-, and 36-month visits) prior to any procedures on the specified visits.

[i] Biopsy 1 may take place between 12 months and 18 months post randomization. Biopsy 2 may take place between 33 months and 39 months post randomization.

[j] Viral serology consists of hepatitis panel (HBsAg, HBsAb, HBcAb, HCV antibody (Ab), if Ab+ then HCV RNA)), HIV-1, HIV-2 antibody screen, and HTLV-1, HTLV-2 antibodies

[k] End-of-Active Phase visit will take place within 30 days following Biopsy 2.

[l] Follow-up visits will start 6 months after the End-of-Active Phase visit.

[m] The early withdrawal visit must occur within 30 days of the last visit.

[n] Risk factors for cardiovascular events will include diabetes mellitus, smoking history, family history, left ventricular hypertrophy, atrial fibrillation, hypertension, myocardial infarction and other cardiovascular disease.

[o] 3-month visit may be completed in the office or via phone.

[p] PSA collected per standard of care, analyzed by local lab.

Study Population and Sample Size

Potential subjects are men ≥18 years that have undergone prostate biopsy and diagnosed with adenocarcinoma of the prostate within the 12 months prior to study Screening. Subjects diagnosed with either ISUP Grade Group 1 or 2 prostate cancer will undergo Screening procedures to ensure that they meet the inclusion and exclusion criteria.

Subjects diagnosed with ISUP Grade Group 1 are required to have a minimum of 3 positive biopsy cores or one core with 50% or more cancer to be eligible for the study.

Subjects diagnosed with ISUP Grade Group 2 will have less than 50% of total number of any cores positive to be eligible for the study. See inclusion criteria 4 for further details.

Subjects will be stratified by 1 or >1 biopsy ≤12 months prior to screening that will balance between arms for the number of prior biopsies and the utilization of MRI guided biopsy for a second or confirmatory biopsy.

Approximately 450 eligible subjects will be randomized 2:1 to either sipuleucel-T arm or control arm. ISUP Grade Group 1 will be capped at 80% of study population.

Stratification will be based on:

- ISUP Grade Group 1 or 2
- Number biopsies 1 or >1 (≤12 months of Screening)

Inclusion Criteria

For a subject to be eligible for participation in this study, *all* of the following criteria must be satisfied.

1. Age is ≥ 18 years
2. Written informed consent provided prior to the initiation of study procedures
3. Histologically proven adenocarcinoma of the prostate initially diagnosed ≤12 months of Screening. All biopsy slides with subject information redacted must be submitted for BICR.
4. Prostate cancer diagnosis determined by BICR as one of the following:
    a. ISUP Grade Group 1 with 3 or more cores positive from a systematic (≥10 cores) biopsy
    b. ISUP Grade Group 1 with ≥ 1 core positive with ≥50% cancer involvement from a systematic (≥10 cores) biopsy

c. ISUP Grade Group 1 from 3 or more positive cores from any combination of cores from a systematic (≥10 cores) biopsy and MRI targeted biopsy (note: multiple cores from each MRI targeted lesion will count as 1 core)

d. ISUP Grade Group 1 from a negative systematic (≥10 cores) biopsy and an MRI targeted core positive with ≥50% cancer involvement

e. ISUP Grade Group 2 from a systematic (≥10 cores) biopsy with <50% of the total number of any cores positive for cancer

f. ISUP Grade Group 2 from a negative systematic (≥10 cores) biopsy and MRI targeted core(s) positive for Gleason 3+4 (see note below)

g. ISUP Grade Group 2 from any combination of cores from a systematic (≥10 cores) biopsy and MRI targeted biopsy (see note below)

Note for f and g: the total number of positive cores must be <50% of total cores from both the systematic biopsy and MRI targeted lesions; each MRI targeted lesion, irrespective of multiple positive cores, will each count as 1 core for the total number of positive cores, e.g., 4 targeted lesions with 2 positive cores each will only add 4 to the total core count.

5. Subject consents to standard of care for biopsy frequency of 2 on-study prostate biopsies and to provide biopsy tissue for study endpoint analysis.

6. Estimated life expectancy ≥ 10 years

7. Candidate for primary curative therapy (e.g., surgery or radiation) if prostate cancer progression occurs

8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

9. Adequate baseline hematologic, renal, and liver function tests as evidenced by laboratory test results within the following ranges ≤30 days prior to randomization

• White blood cell (WBC) count	≥ 3.0 x 10^6 cells/mL
• Absolute neutrophil count (ANC)	≥ 1.5 x 10^6 cells/mL
• Platelet count	≥ 1.0 x10^5 cells/μL
• Hemoglobin (Hgb)	≥ 10.0 g/dL
• Creatinine	≤ 1.5 mg/dL
• Total bilirubin	≤ 1.5 x upper limit of normal (ULN)
• Alanine aminotransferase (ALT)	≤ 2.0 x ULN
• Aspartate aminotransferase (AST)	≤ 2.0 x ULN

Exclusion Criteria

A subject will not be eligible for participation in this study if *any* of the following criteria apply.

1. Former therapy for prostate cancer (local or systemic)
2. Any previous prostatic surgical procedure that significantly changes the anatomy of prostate (at the discretion of sponsor's Medical Monitor)
3. Any investigational product received for prostate cancer
4. Prostate biopsy specimen reveals neuroendocrine or small cell features
5. Primary Gleason score is ≥ 4 or any Gleason pattern 5
6. Any evidence of locally advanced, regional or metastatic disease, including regional and distant lymph node enlargement (Nodes ≥1.5 cm in the short axis are considered pathologic and measurable) (Scher, 2016)
7. A history of a cerebrovascular event (CVE) or transient ischemic attack (TIA)
8. Subject has used a 5-alpha-reductase inhibitor (e.g., finasteride or dutasteride) continuously for ≥ 6 months and within 6 months prior to study Screening
9. Subject has a history of any other stage I-IV malignancy, except for basal or squamous cell skin cancer. The subject must be disease free and off any malignancy-related treatment for at least 5 years.
10. Subject has prior use within 30 days of study Screening of any herbal, dietary, or alternative anti-cancer treatment or product, such as PC-SPES (or PC-x product), saw palmetto, ketoconazole, an estrogen-containing nutraceutical, or high dose calcitriol (>0.5 µg/day). The Investigator will consider herbal therapies on a case-by-case basis to determine whether they fall into the category of prohibited medications based on their potential for hormonal or anti-cancer or anti-cancer properties.
11. Need for systemic chronic immunosuppressive therapy (e.g., anti-tumor necrosis factor alpha monoclonal antibodies, glucocorticoids)
12. Uncontrolled, concurrent illness including, but not limited to the following: ongoing or active infection (bacterial, viral, or fungal), symptomatic congestive heart failure (New York Classification III-IV) (Appendix 6) or unstable angina pectoris within the last 6 months, or psychiatric illness that would limit compliance with study requirements as well as any condition that would preclude a subject from undergoing leukapheresis (e.g., within the previous 6 months: myocardial infarction, interventional cardiology procedure such as angioplasty or stent placement, pulmonary embolism or deep vein thrombosis).

13. Hypogonadal (T < 175 ng/dL) or on continuous testosterone replacement therapy

14. Positive serology for HIV-1, HIV-2 or HTLV-1, HTLV-2

15. Active hepatitis B or C (See Appendix 8 and Appendix 9 for definitions)

16. Any medical intervention, any other condition, or any other circumstance which, in the opinion of the investigator or the sponsor's Medical Monitor, could compromise adherence with study requirements or otherwise compromise the study's objectives.

Statistical Considerations

The Phase 3, open-label study is designed to assess the effects of sipuleucel-T in subjects on AS. The primary endpoint will analyze approximately 450 subjects randomized (2:1 sipuleucel-T arm versus control arm).

It is estimated that the proportion of increased histopathologic grade reclassification over the 36 months following randomization for the control arm will be approximately 0.30. While there is no prior information on sipuleucel-T treatment response in early-stage disease available, a meaningful hypothesized reduction in this proportion is a reduction by 0.14, giving a projected outcome proportion of upgrading in the sipuleucel-T arm of 0.16. The null hypothesis of both arms having a proportion of 0.70 (= 1- 0.30) being free from upgrading at 36 months versus the specific alternative hypothesis of a sipuleucel-T arm outcome of 0.84 (= 1- 0.16). The odds ratio associated with the specific alternative hypothesis is 2.25 (sipuleucel-T arm odds over control arm odds). Based on an overall 1-sided alpha of 0.025 approximately 300 subjects in the sipuleucel-T arm and 150 subjects in the control arm will provide 90% power to demonstrate the superiority of sipuleucel-T to control.

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ADT	androgen deprivation therapy
AE	adverse event
ALT	alanine aminotransferase
AOR	additional optional research
APC	antigen presenting cells
AS	active surveillance
AST	aspartate aminotransferase
BICR	blinded independent central review
COI	chain of identity
CTCAE	Common Terminology Criteria for Adverse Events
CVE	cerebrovascular event
DRE	digital rectal exam
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
EPIC-CP	The Expanded Prostate Cancer Index Composite for Clinical Practice
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
GM-CSF	granulocyte-macrophage colony-stimulating factor
H&E	hematoxylin and eosin
HIV-1	human immunodeficiency virus type 1
HIV-2	human immunodeficiency virus type 2
HTLV-1	human T-lymphotropic virus type 1
HTLV-2	human T-lymphotropic virus type 2
ICF	informed consent form
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IMF	immunotherapy manufacturing facility
IND	Investigational New Drug
IPSS	International Prostate Symptom Score
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISUP	International Society of Urological Pathology
ITT	intent-to-treat
mCRPC	metastatic castration-resistant prostate cancer
MAX-PC	Memorial Anxiety Scale for Prostate Cancer
mpMRI	multiparametric magnetic resonance imaging
OS	overall survival
NCI	National Cancer Institute
NK	natural killer cells
PAP	prostatic acid phosphatase
PA2024	recombinant fusion protein composed PAP linked to GM-CSF

PCa	prostate cancer
PBMC	peripheral blood mononuclear cells
PE	physical examination
PRO	patient-reported outcome
PSA	prostate specific antigen
SAE	serious adverse event
SF-12	Short Form 12 Health Survey
TIA	transient ischemic attack
TNC	total nucleated cell
ULN	upper limit of normal
WBC	white blood cell

1.0 REGULATORY AND GOOD CLINICAL PRACTICE REQUIREMENTS

1.1 Pre-Study Documentation

Prior to site activation in order for a clinical trial site to be able to start screening the first subject, sponsor or designee must receive:

- Signed protocol and Investigator Brochure signature pages
- Signed Form FDA 1572 Statement of Investigator
- Current curriculum vitae for Investigators
- Current medical license(s) for Investigators
- Signed financial disclosure form from Investigators
- Institutional Review Board (IRB) approval letter for the protocol, informed consent form(s) (ICFs), and materials for subject information and recruitment, as applicable
- IRB-approved ICFs
- IRB membership listing or Department of Health and Human Services (DHHS) Assurance Number

All documentation must be updated as applicable throughout the study.

1.2 Institutional Review Board

The Principal Investigator is responsible for ensuring that this protocol and relevant supporting information are submitted to the appropriate IRB for review and approval before the study is initiated. 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 and should be provided with a summary of the results of the study as required by the IRB.

1.3 Investigator Obligations

The Principal Investigator will ensure all clinical trial site personnel conduct the study in compliance with ethical principles contained within the Declaration of Helsinki, the International Conference on Harmonization (ICH) E6(R2) Guideline for Good Clinical Practice (GCP), and the Food and Drug Administration (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 with the study protocol, and must meet periodically with the sponsor or designee's study monitor.

All investigators listed on Form FDA 1572 must complete financial disclosure forms (including information on spouses, legal partners, and/or dependent children). 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. Investigators must also complete a new financial disclosure form throughout the study per sponsor or designee's requirement, regardless of whether any information has changed.

In addition, the Principal Investigator is responsible for providing the sponsor or designee an adequate final report shortly after study participation is complete.

1.4 Informed Consent

Investigators are responsible for obtaining written informed consent from subjects prior to initiation of any study procedures. The investigator or an appropriately qualified delegate will obtain informed consent, document the steps of the informed consent process in the subject's medical record, and provide a copy of the signed ICF to the subject.

The ICF, including any amendments, must first be reviewed and approved by the sponsor or designee 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 informed 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 informed consent from any new subject who is enrolled in the study after the IRB approval date of the amendment.

1.5 Subject Confidentiality

Subjects' medical information obtained as a result of this study is considered confidential, as defined by applicable local, state, and federal law, and disclosure of this information to third parties other than those noted below is prohibited. Subject identifiers (e.g., name, initials, or date of birth) will be kept confidential. A subject's medical information may be given to the subject's personal physician or 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 or other regulatory authorities, sponsor or its representatives, or the IRB. Sponsor or designee may retain subjects' medical information with subject identifiers redacted.

Subject identifiers will not be collected on electronic case report forms (eCRFs) maintained by the sponsor or designee with the exception of date of birth and the Chain of Identity (COI) number of each sipuleucel-T infusion. Subject identifiers will not be disclosed in any publication related to this study.

Because sipuleucel-T is an autologous product, a unique COI number for each sipuleucel-T product must be maintained from the time of initial collection of blood during leukapheresis until infusion, to ensure each subject receives the correct product. Dendreon uses a COI number and the subject's full name and date of birth for this purpose. The COI for sipuleucel-T begins when the subject is scheduled for sipuleucel-T infusion and is referenced during leukapheresis, maintained through the manufacturing process, and finally, referenced prior to infusion. The COI number and subject's full name and date of birth will be revealed to Dendreon scheduling, manufacturing, and leukapheresis personnel. This disclosure is critical to ensuring subjects' safety.

2.0 INTRODUCTION

2.1 Background

2.1.1 Prostate Cancer

In the United States, an estimated 164,690 cases of prostate cancer will be diagnosed in 2018 (Siegel, 2018). However, many of these men will have disease that may never cause morbidity or mortality due to their diagnosis of prostate cancer. Therefore, the management of newly diagnosed, localized prostate cancer detected on the basis of prostate-specific antigen (PSA) remains controversial. Recently, Cooperberg et al. showed a shift from initial active treatment (e.g., surgery, radiation) to choosing AS (Cooperberg, 2015). Active surveillance (AS) delays or indefinitely postpones the complications of surgery, radiation or androgen deprivation therapy (ADT), while allowing for subsequent interventional treatment with similar clinical efficacy associated with immediate treatment (Dall'Era, 2017). Men on AS are advised to adhere to follow-up protocols and schedules (Borkhorst, 2015), yet 25% to 45% of men were no longer on AS after 5 to 15 years of follow-up (Klotz, 2015). The most common reasons for discontinuing AS were PSA-doubling time (43.5%), grade progression (35%) patient preference (6%), and stage progression (3%) (Klotz, 2015). Recently, the PRIAS study investigators concluded Gleason upgrading and disease re-classification (≥cT3) as the only indicators for an immediate switch to active treatment. Surrogate indicators such as number of positive cores and a PSA-doubling time of <3 years should not trigger immediate active treatment but instead continued follow-up to confirm higher-risk disease (Borkhorst, 2016). Thus histopathologic progression is an important indicator for prostate cancer progression and the need for treatment, and decreasing histopathologic progression would be a significant benefit for the AS prostate cancer population.

2.1.2 Sipuleucel-T

Sipuleucel-T is an autologous cellular immunotherapy available as a suspension for intravenous infusion. Sipuleucel-T consists of autologous peripheral blood mononuclear cells (PBMC), including antigen presenting cells (APCs) that have been activated during a defined culture period with a recombinant human protein, PAP-GM-CSF, consisting of prostatic acid phosphatase (PAP), an antigen expressed in prostate cancer tissue, linked to granulocyte-macrophage colony-stimulating factor (GM-CSF), an immune cell activator. Each dose of

sipuleucel-T contains a minimum of 50 million autologous CD54+ cells activated with PAP-GM-CSF, suspended in 250 mL of Lactated Ringer's Injection, USP.

The active components of sipuleucel-T are autologous APCs and PAP-GM-CSF. During culture, the recombinant antigen binds to and is processed by APCs into smaller peptide fragments. The recombinant antigen is designed to target APCs, and may help direct the immune response to PAP. Minimal residual levels of the intact PAP-GM-CSF are detectable in the final sipuleucel-T product.

The patient's PBMCs are obtained via a standard leukapheresis procedure approximately 3 days prior to the infusion date. Due to the autologous nature of sipuleucel-T, it is important that the patient and physician adhere to the personalized leukapheresis and infusion schedules.

The cellular composition of sipuleucel-T is dependent on the composition of cells obtained from the patient's leukapheresis. In addition to APCs, the final product contains T cells, B cells, natural killer (NK) cells, and other cells. The number of cells present and the cellular composition of each sipuleucel-T dose will vary.

The potency of sipuleucel-T is in part determined by measuring the increased expression of the CD54 molecule, also known as ICAM-1, on the surface of APCs after culture with PAP-GM-CSF. CD54 is a cell surface molecule that plays a role in the immunologic interactions between APCs and T cells, and is considered a marker of immune cell activation.

In-process and final sterility tests are initiated prior to shipping, but the final results are not available for up to 7 days. Sipuleucel-T is released for shipping based on acceptable results from 2-day incubation of the in-process sterility test (Sipuleucel-T, 2017).

Sipuleucel-T induces robust and long-lived antigen-specific cellular and humoral immune responses that target prostate cancer cells. The magnitude of the immune response correlates with overall survival (OS) in subjects with metastatic castration-resistant prostate cancer (mCRPC) (Sheikh, 2013).

Sipuleucel-T administered to subjects prior to radical prostatectomy demonstrated both a systemic antigen-specific T cell response and a local response with the recruitment of activated effector T cells into the prostate tumor microenvironment (Fong, 2014). In subjects with non-metastatic hormone-sensitive prostate cancer, the magnitude of immunoglobulin G responses to antigen was significantly higher, and the magnitude of secondary antibody responses (antigen spread), as well as APC activation was significantly greater when compared to subjects with mCRPC (Antonarakis, 2017). These data suggest sipuleucel-T may have a more robust anti-cancer effect in non-metastatic hormone-sensitive prostate cancer subjects and the potential to slow or inhibit the development of more aggressive disease requiring treatment for men on AS.

The purpose of this study is to determine if sipuleucel-T will decrease the development of histopathologic progression upon subsequent prostate biopsies for subjects on AS.

3.0 STUDY OBJECTIVES

3.1 Primary Objective

- To assess the efficacy of sipuleucel-T in reducing histopathologic reclassification to a higher Gleason grade in prostate cancer subjects on active surveillance (AS)

3.2 Secondary Objectives

- To assess the differential receipt of local or systemic therapy (surgery, radiation, ADT) in each study arm, and the reasons for receipt of further local or systemic therapy
- To assess differences in quality of life (i.e., patient-reported outcomes (PRO)) between sipuleucel-T and control arms
- To evaluate the safety of sipuleucel-T in men with low to intermediate risk localized prostate cancer

3.3 Exploratory Objectives

- To evaluate in the sipuleucel-T arm the association of peripheral blood and tumor microenvironment immunologic responses with reclassification of Gleason grade over time
- To evaluate clinical assessments and potential correlation to sipuleucel-T
- To evaluate prostate tissue genomics

4.0 STUDY ENDPOINTS

4.1 Primary Endpoint

- Proportion of subjects without histological reclassification (Gleason group upgrade) within 36 months of randomization as determined by Blinded Independent Central Review (BICR)
    - Upgrade is defined as subjects at randomization with either International Society of Urological Pathology (ISUP) Grade Group 1 (Gleason 3+3) upgraded to Grade Group 2 (Gleason 3+4) or higher or subjects at randomization with Grade Group 2 upgraded to Grade Group 3 (Gleason 4+3) or higher.

4.2 Secondary Endpoints

- To determine the number of subjects with subsequent prostate cancer treatment (e.g., surgery, radiation, ADT) in each study arm
- Characterization of PROs by Memorial Anxiety Scale for Prostate Cancer (MAX-PC), Short Form 12 Health Survey (SF-12), The Expanded Prostate Cancer Index Composite

for Clinical Practice (EPIC-CP), International Prostate Symptom Score (IPSS) at baseline and 12-, 24-, and 36-month visits after randomization

- To evaluate safety by determining the incidence of adverse events (AEs), assessing laboratory data for clinically significant laboratory abnormalities and evaluating physical examination (PE) findings in each study arm

4.3 Exploratory Endpoints

- To calculate the correlation of prostate tissue and peripheral immune responses as well as product parameters to sipuleucel-T efficacy
- To determine in the cohort of subjects having a radical prostatectomy the number subjects with an ISUP Grade Group change (up- or down-grade) determined by BICR from radical prostatectomy tissue histology in each study arm
- To measure the percentage of subjects with a negative biopsy at any post- randomization biopsy assessment in each study arm
- To compare the proportion of subjects with clinical risk group progression (e.g., Cancer of the Prostate Risk Assessment (CAPRA) and National Comprehensive Cancer Network (NCCN) prostate cancer risk groups) between study arms
- To calculate Prostate-specific antigen (PSA) velocity from randomization through study completion in each study arm
- To determine the association of prostate cancer tissue genomic profile and sipuleucel-T treatment

5.0 INVESTIGATIONAL PLAN

5.1 Study Design and Duration

This is a multicenter, randomized, open-label study of immunotherapy with sipuleucel-T compared to control subjects followed on AS. The study will enroll subjects being followed by AS and initially diagnosed within 12 months prior to Screening with either ISUP Grade Group 1 or 2 adenocarcinoma of the prostate.

This study consists of 3 phases (see Section 8.0 for more details):

Screening Phase:

The Screening Phase will begin at the completion of the informed consent process and continues until randomization. Screening procedures will be performed up to 30 days prior to randomization.

The following assessments will be performed on all subjects during the Screening Phase:

- BICR of prostate biopsy slides obtained from local pathologist (ISUP Grade Group and Gleason Score)
- Clinical evaluations (demographics, medical history, PE & vital signs, digital rectal examination (DRE), Eastern Cooperative Oncology Group (ECOG) performance status, cardiovascular risk assessment & electrocardiogram (ECG))
- Cardiovascular and thrombosis disease history
- Concomitant medications
- All anti-prostate cancer therapies
- PROs/Quality of life questionnaires
- Virology serology (HBsAg, HBsAb, HBcAb, HCV antibody(Ab), if Ab positive (Ab+) then HCV RNA)), HIV-1 and HIV-2 antibody screen and HTLV-1, HTLV-2 antibodies
- Hematology and chemistry
- PSA
- Total testosterone

Active Phase:

The Active Phase will begin at randomization and continues through completion of the end of Active Phase study visit (within 30 days of Biopsy 2) or until the study is terminated by the sponsor. Subjects who withdraw consent and discontinue from the study prior completing end of Active Phase study visit will undergo an Early Withdrawal visit within 30 days following discontinuation notice (Section 6.3). Subjects are encouraged to have, as standard of care, a systematic prostate biopsy (≥10 cores) with or without MRI at the investigator's discretion prior to study withdrawal. The H&E and special-stained slides from this biopsy will be submitted for BICR determination of their ISUP Grade Group classification prior to study withdrawal

After Screening assessments are completed, eligible subjects will be randomized 2:1 to the sipuleucel-T arm or the control arm. Subjects randomized to sipuleucel-T arm will undergo their first leukapheresis within 60 days of randomization and will receive 3 infusions of sipuleucel-T at approximately 2-week intervals. Subjects randomized to the control arm will be followed on AS as described in the schedule of events (Table 2).

Subjects randomized to the sipuleucel-T arm will be evaluated at 0, 2, 4, 6, 10, 14, and 26 weeks following the first infusion for:

- Immune responses (Week 0 prior to first infusion is baseline)
- All anti-prostate cancer therapies
- Concomitant medications
- Adverse events (AEs) and serious adverse events (SAEs) (per reporting requirements for the sipuleucel-T arm) (Section 9)

Subjects randomized to the control arm will be evaluated (office visit or phone) at 3 months following randomization for:

- Survival status
- All anti-prostate cancer therapies
- Concomitant medications
- All AEs and SAEs

Subsequently, all subjects in the sipuleucel-T and control arms will be followed every 6 months from date of randomization for at least 36 months for:

- Immune responses (sipuleucel-T arm only)
- Survival status
- PSA levels (should be collected prior to DRE and biopsy procedures)
- DRE assessments
- Prostate cancer disease progression
- All anti-prostate cancer therapies
- Concomitant medications
- All AEs and SAEs

Note, for subjects randomized to the sipuleucel-T arm, scheduled events for the 26-week visit post first infusion and first 6-month visit post randomization may take place on the same visit and only one set of immune samples need to be collected.

During the Active Phase, all subjects in the sipuleucel-T and control arms will complete:

- PROs/Quality of life questionnaires (Max-PC, SF-12, EPIC-CP, and IPSS) annually (12-, 24-, and 36-month visits) post randomization. PROs/Quality of life questionnaires should be collected prior to any procedures on these specified visits.

- Two (2) systematic biopsies (Biopsy 1 & Biopsy 2; ≥10 cores each)) will be administered as standard of care. Additional cores may be collected by MRI guidance per investigator discretion; however, MRI targeted cores collected at baseline should be repeated for Biopsy 1 & Biopsy 2 (Appendix 7).

Biopsy 1 will be administered between 12 and 18 months, and Biopsy 2 will be administered between 33 and 39 months post randomization. All hematoxylin and eosin (H&E) and special stained slides will be assessed for histopathologic grading by BICR. Slides from each biopsy will be considered as a group to determine the ISUP Grade Group as opposed to any single slide. The BICR is blinded to a subject's study arm randomization. BICR will receive the local pathology staining methods and Gleason score. All subject information should be redacted from the local pathology reports and slides. Local pathology reports and slides will be identified only by study subject number. All slides will be returned to the clinical trial site.

Post randomization, central pathology requested formalin-fixed paraffin-embedded (FFPE) tissue blocks identified by study subject number will be sent to the central pathology lab for cutting and slide preparation for immunohistochemistry (IHC) and genomic analysis. All tissue blocks will be returned to the clinical trial site.

Follow-up Phase:

Once a subject from either the sipuleucel-T or control arms completes the end of Active Phase visit, they will enter into Follow-up Phase and will complete Follow-up Phase visits every 6 months starting from their last Active Phase visit. The Follow-up Phase end when the last subject enrolled completes Biopsy 2 and end of Active Phase visit or until the study is terminated by the sponsor. All subjects will be assessed for:

- Survival status

- PROs/Quality of life questionnaires

- PSA levels (as available by local laboratory)

- Prostate cancer disease progression

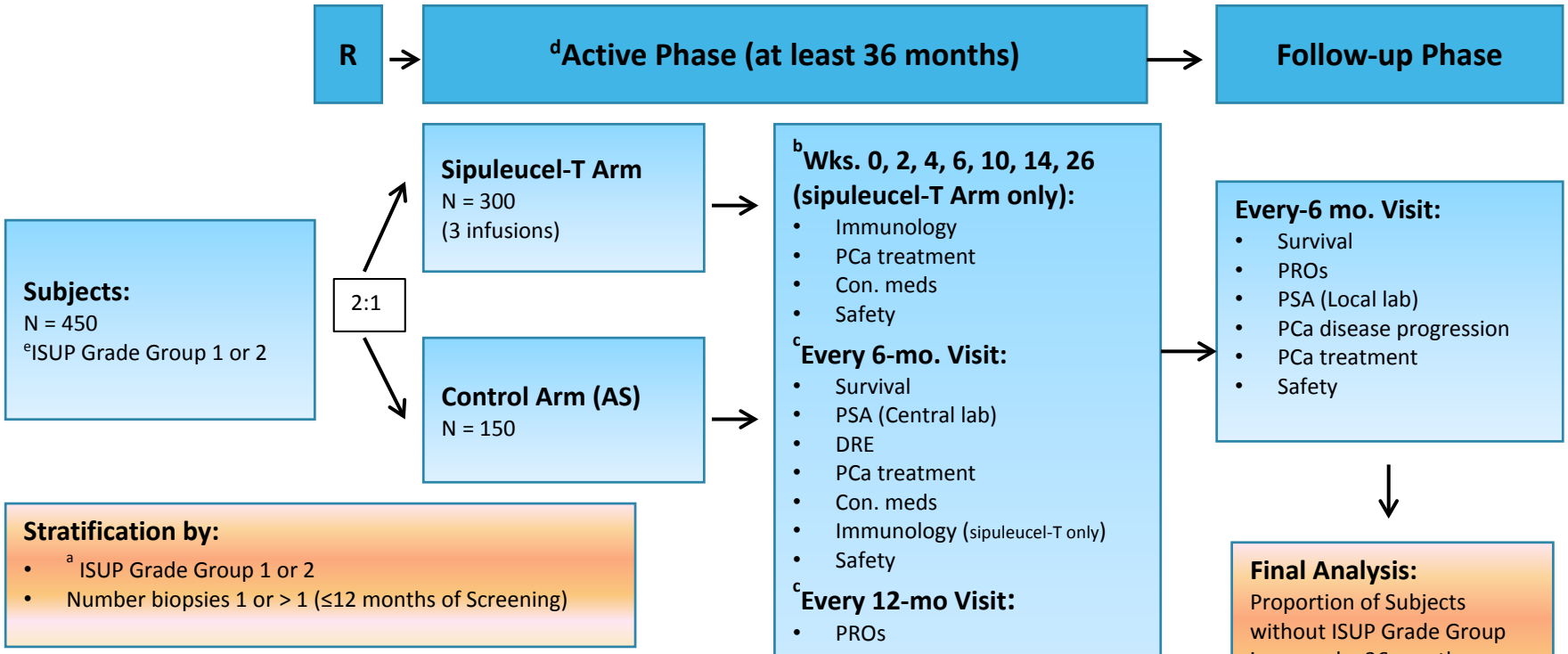
- All anti-prostate cancer therapies

- AEs and SAEs (per reporting requirements for each arm; Section 9)

Upon completion of the study, if the primary endpoint is met, subjects on the control arm may be offered sipuleucel-T.

The figure below presents a schematic of the study design.

Figure 1: Study Schematic



[a] Epstein JI, Am J Surg Pathol, 2017

[b] Weeks from **first infusion**; Sipuleucel-T arm only; 26 wk. & 6-mo. visit may occur same day

[c] Months from **randomization in both arms**

[d] Active Phase ends when the last subject enrolled completes 36-mo. Biopsy and end of Active Phase visit

[e] International Society Urological Pathology (ISUP); Grade Group 1 = Gleason 3+3; Grade Group 2 = Gleason 3+4

[f] Immunohistochemistry (IHC)

6.0 STUDY POPULATION

Potential subjects are men ≥18 years that have undergone prostate biopsy and diagnosed with adenocarcinoma of the prostate within 12 months prior to study Screening. Subjects diagnosed with either ISUP Grade Group 1 or 2 prostate cancer will undergo screening procedures to ensure that they meet the inclusion and exclusion criteria.

Subjects diagnosed with ISUP Grade Group 1 are required to have a minimum of 3 positive biopsy cores or one core with 50% or more cancer to be eligible for the study.

Subjects diagnosed with ISUP Grade Group 2 will have less than 50% of total number of any cores positive to be eligible for the study. See inclusion criteria 4 for further details.

Subjects will be stratified by 1 or >1 biopsy ≤12 months prior to screening that will balance between arms for the number of prior biopsies and the utilization of MRI guided biopsy for a second or confirmatory biopsy.

Approximately 450 eligible subjects will be randomized 2:1 to either sipuleucel-T arm or control arm. ISUP Grade Group 1 will be capped at 80% of study population.

Stratification will be based on:

- ISUP Grade Group 1 or 2
- Number biopsies 1 or >1 (≤12 months of Screening)

6.1 Inclusion Criteria

For a subject to be eligible for participation in this study, *all* of the following criteria must be satisfied.

6.1.1. Age is ≥ 18 years

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

6.1.3. Histologically proven adenocarcinoma of the prostate initially diagnosed ≤12 months of Screening. All biopsy slides with subject information redacted must be submitted for BICR.

6.1.4. Prostate cancer diagnosis determined by BICR as one of the following:

a. ISUP Grade Group 1 with 3 or more cores positive from a systemic (≥10 cores) biopsy.

b. ISUP Grade Group 1 with ≥1 core positive with ≥50% cancer involvement from a systematic (≥10 cores) biopsy

c. ISUP Grade Group 1 from 3 or more positive cores from any combination of cores from a systematic (≥10 cores) biopsy and MRI targeted biopsy (note: multiple cores from each MRI targeted lesion will count as 1 core)

d. ISUP Grade Group 1 from a negative systematic (≥10 cores) biopsy and an MRI targeted core positive with ≥50% cancer involvement

e. ISUP Grade Group 2 from a systematic (≥10 cores) biopsy (with<50% of the total number of any cores positive for cancer

f. ISUP Grade Group 2 from a negative systematic (≥10 cores) biopsy and MRI targeted core(s) positive for Gleason 3+4 (see note below)

g. ISUP Grade Group 2 from any combination of cores from a systematic (≥10 cores) biopsy and MRI targeted biopsy (see note below)

Note for f and g: the total number of positive cores must be <50% of total cores from both the systematic biopsy and MRI targeted lesions; each MRI targeted lesion, irrespective of multiple positive cores, will each count as 1 core for the total number of positive cores, e.g., 4 targeted lesions with 2 positive cores each will only add 4 to the total core count).Subject consents to standard of care for biopsy frequency of 2 on-study prostate biopsies and to provide biopsy tissue for study endpoint analysis.

6.1.5. Estimated life expectancy ≥ 10 years

6.1.6. Candidate for primary curative therapy (e.g., surgery or radiation) if prostate cancer progression occurs

6.1.7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

6.1.8. Adequate baseline hematologic, renal, and liver function tests as evidenced by laboratory test results within the following ranges ≤30 days prior to randomization

- White blood cell (WBC) count ≥ 3.0 x 10^6 cells/mL
- Absolute neutrophil count (ANC) ≥ 1.5 x 10^6 cells/mL
- Platelet count ≥ 1.0 x10^5 cells/μL
- Hemoglobin (Hgb) ≥ 10.0 g/dL
- Creatinine ≤ 1.5 mg/dL
- Total bilirubin ≤ 1.5 x upper limit of normal (ULN)
- Alanine aminotransferase (ALT) ≤ 2.0 x ULN
- Aspartate aminotransferase (AST) ≤ 2.0 x ULN

6.2 Exclusion Criteria

A subject will not be eligible for participation in this study if *any* of the following criteria apply.

6.2.1. Former therapy for prostate cancer (local or systemic)

6.2.2. Any previous prostatic surgical procedure that significantly changes the anatomy of prostate (at the discretion of sponsor's Medical Monitor)

6.2.3. Any investigational product received for prostate cancer

6.2.4. Prostate biopsy specimen reveals neuroendocrine or small cell features

6.2.5. Primary Gleason score is ≥ 4 or any Gleason pattern 5

6.2.6. Any evidence of locally advanced, regional or metastatic disease, including regional and distant lymph node enlargement (Nodes ≥1.5 cm in the short axis are considered pathologic and measurable) (Scher, 2016)

6.2.7. A history of a cerebrovascular event (CVE) or transient ischemic attack (TIA)

6.2.8. Subject has used a 5-alpha-reductase inhibitor (e.g., finasteride or dutasteride) continuously for ≥ 6 months and within 6 months prior to study Screening

6.2.9. Subject has a history of any other stage I-IV malignancy, except for basal or squamous cell skin cancer. The subject must be disease free and off any malignancy-related treatment for at least 5 years.

6.2.10. Subject has prior use within 30 days of study Screening of any herbal, dietary, or alternative anti-cancer treatment or product, such as PC-SPES (or PC-x product), saw palmetto, ketoconazole, an estrogen-containing nutraceutical, or high dose calcitriol (>0.5 µg/day). The Investigator will consider herbal therapies on a case-by-case basis to determine whether they fall into the category of prohibited medications based on their potential for hormonal or anti-cancer or anti-cancer properties.

6.2.11. Need for systemic chronic immunosuppressive therapy (e.g., anti-tumor necrosis factor alpha monoclonal antibodies, glucocorticoids)

6.2.12. Uncontrolled, concurrent illness including, but not limited to the following: ongoing or active infection (bacterial, viral, or fungal), symptomatic congestive heart failure (New York Classification III-IV) (Appendix 6) or unstable angina pectoris within the last 6 months, or psychiatric illness that would limit compliance with study requirements as well as any condition that would preclude a subject from undergoing leukapheresis (e.g., within the previous 6 months: myocardial infarction, interventional cardiology procedure such as angioplasty or stent placement, pulmonary embolism or deep vein thrombosis).

6.2.13. Hypogonadal (T < 175 ng/dL) or on continuous testosterone replacement therapy

6.2.14. Positive serology for HIV-1, HIV-2 or HTLV-1, HTLV-2

6.2.15. Active hepatitis B or C (See Appendix 8 and Appendix 9 for definitions)

6.2.16. Any medical intervention, any other condition, or any other circumstance which, in the opinion of the investigator or the sponsor's Medical Monitor, could compromise adherence with study requirements or otherwise compromise the study's objectives.

6.3 Discontinuation from Study

A subject may discontinue 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 eCRF.

Whenever possible, every subject who withdraws consent and discontinues from the study will undergo an Early Withdrawal Visit within 30 days following discontinuation notice. Subjects are encouraged to have, as standard of care, a systematic prostate biopsy (≥10 cores) with or without MRI at the investigator's discretion prior to study withdrawal. The H&E and special-stained slides from this biopsy will be submitted for BICR determination of their ISUP Grade Group classification prior to study withdrawal. All AEs considered by the investigator to be related to sipuleucel-T that are ongoing at the time of discontinuation will be followed by the investigator until resolution, return to baseline, or a determination by the investigator that no further improvement is expected. The investigator should make every reasonable attempt to ensure that the subject is contacted (via telephone or during the Early Withdrawal Visit) to obtain the final status of any AEs and concomitant medications.

6.3.1 Discontinuation from Sipuleucel-T Arm

Declining the first sipuleucel-T infusion or associated leukapheresis will result in an automatic withdrawal from the study. Subjects will complete an early withdraw visit within 30 days of the scheduled sipuleucel-T infusion.

Sipuleucel-T will be discontinued if a subject meets any of the following criteria:

- The subject never undergoes a leukapheresis for the purpose of receiving sipuleucel-T
- The subject undergoes leukapheresis, but is unable to receive at least 1 partial (>0 mL) sipuleucel-T infusion for any reason at the discretion of sponsor's Medical Monitor
- Inability to manufacture sipuleucel-T in the opinion of the sponsor's medical monitor
- The subject experiences intolerable toxicity
- Significant infection at the discretion of sponsor's Medical Monitor

- CVE or TIA of any grade prior to completion of 3 sipuleucel-T infusions
- Withdrawal of consent for continued sipuleucel-T infusions
- The subject fails to comply with protocol-specified procedures or protocol requirements
- Sponsor terminates the study
- The subject is discontinued from the study at the discretion of the investigator or sponsor

6.3.2 Discontinuation from Study Participation

A subject in either the sipuleucel-T or control study arms will end study participation, including discontinuation of sipuleucel-T (sipuleucel-T arm only), biopsy and blood sample collection, for any of the following reasons:

- The subject withdraws consent or loses the ability to provide informed consent to participate in the study for any reason
- The subject is diagnosed with locally advanced or metastatic prostate cancer
- The subject dies or is lost to follow-up (Section 6.5)

6.4 Replacement of Subjects

Subjects who are randomized to the sipuleucel-T arm, but do not receive any sipuleucel-T (>0 mL) may be replaced.

6.5 Lost to Follow-up

If a subject fails to respond to requests for follow-up, the clinical trial site will send a certified 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 subject's medical record. Subjects who do not respond to requests for follow-up after all the above attempts to establish contact will be considered lost to follow-up.

6.6 Permitted Therapies

Subjects should receive full supportive care in accordance with standard practice at the clinical trial site.

Subjects who are receiving non-prostate cancer therapies (prescription or over-the-counter) at the time of randomization (that are not restricted (Section 6.7) should continue per the discretion of the prescribing physician.

6.7 Restricted Therapies During Sipuleucel-T Treatment Period

Certain therapies and procedures could confound the results of this study. Therefore, subjects who are randomized to the sipuleucel-T arm and receive any of the following, 30 days prior to the first infusion until 30 days after the last infusion, will discontinue sipuleucel-T treatment (Section 6.3.1):

- Any immunosuppressive therapy, including systemic steroids. 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
- Blood products
- GM-CSF or G-CSF
- Any vaccinations

Subjects that discontinue sipuleucel-T treatment and have received > 0 mL of sipuleucel-T will remain in the Active Phase and follow the schedule of events (Table 1).

6.8 Restricted Therapies from Randomization to End of Active Phase (Sipuleucel-T and Control Arms)

Certain therapies and procedures could confound the results of this study. Therefore, subjects who receive any of the following will go from Active Phase of the study to the Follow-up Phase of the study:

- Any local or systemic therapy or procedures for prostate cancer (e.g., ADT, radical prostatectomy, external beam radiation or brachytherapy)
- Any local or systemic therapy or procedure targeting the prostate (e.g., transurethral resection of the prostate (TURP) or 5-alpha reductase inhibitor)
- Major surgery at the discretion of the sponsor's Medical Monitor
- Any investigational product for prostate cancer or other condition (per sponsor's Medical Monitor approval)
- Any other therapy at the discretion of the sponsor's Medical Monitor

7.0 SIPULEUCEL-T TREATMENT

7.1 Overview

Dendreon will supply sipuleucel-T that must be stored, handled, prepared, administered, and labeled as specified by the current version of the sipuleucel-T Investigator's Brochure.

Accountability documentation must be maintained to ensure that sipuleucel-T is accurately administered. Such documentation will note request, shipment, receipt, storage, dispensation, administration, destruction, return, and use of required processes.

7.2 Sipuleucel-T Treatment

7.2.1 Leukapheresis and Infusion Scheduling

Once a subject has completed screening assessments and has been confirmed to be eligible and randomized to the sipuleucel-T arm, Dendreon will designate a leukapheresis center and the site will request a schedule for the subject's leukapheresis procedures to occur at approximately 2-week intervals. The date of each leukapheresis procedure will determine the date for the subsequent infusion of sipuleucel-T (approximately 3 days later).

The clinical trial site will receive confirmation of the leukapheresis and infusion dates and will schedule the subject's infusion appointments accordingly. If the subject is subsequently deemed ineligible for the study, the clinical trial site will be informed and the leukapheresis and infusion appointments will be canceled.

7.2.2 Pre-leukapheresis Assessments

Prior to each leukapheresis, subjects will undergo a pre-leukapheresis assessment to determine their suitability for the leukapheresis procedure. The pre-leukapheresis assessments including any requested tests by the apheresis center should be done within 7 days prior to each leukapheresis.

If a subject has any infection requiring parenteral antibiotic therapy or causing fever (temperature > 100.5°F or > 38.1°C) within 7 days 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.

7.2.3 Subject Preparation for Leukapheresis

The subject should be instructed to eat calcium-rich foods in advance of the leukapheresis procedure. The subject should also be instructed to drink plenty of fluids a few days prior to the procedure to promote adequate venous access during leukapheresis, but to avoid drinking caffeinated beverages on the day of each leukapheresis procedure.

7.2.4 Leukapheresis

To manufacture of one dose of sipuleucel-T, the subject will undergo leukapheresis in order to collect PBMC. All PBMC collected from one leukapheresis procedure will be used to produce one dose of sipuleucel-T. Immediately after completion of the leukapheresis procedure, the PBMC are transported to a Dendreon immunotherapy manufacturing facility (IMF).

7.2.5 Sipuleucel-T Infusion

Each sipuleucel-T product is released by Dendreon for infusion approximately 3 days after the leukapheresis procedure. The clinical trial site will provide all supplies required for infusion.

Sipuleucel-T must be administered under the supervision of an investigator experienced in the medical treatment of prostate cancer and in an environment where resuscitation equipment is available.

7.2.6 Sipuleucel-T Product Failures and Leukapheresis Rescheduling

A subject may be scheduled for a repeat leukapheresis procedure if the subject's leukapheresis procedure fails, sipuleucel-T does not meet quality release specifications, sipuleucel-T infusion is not started prior to its expiration, or for various other reasons. Rescheduling will depend upon the capacities of the leukapheresis center and the Dendreon IMF, and ≥ 2 weeks should elapse between one leukapheresis procedure and the next (1-week interval may be approved at the discretion of the Medical Monitor).

If a subject's subsequent leukapheresis procedure is delayed or rescheduled for any reason, all protocol-specified pre-leukapheresis assessment conditions apply.

In rare instances, it may be determined for a given subject that it is not possible to manufacture sipuleucel-T that meets manufacturing release specifications (Section 6.3.1).

7.3 Timing of Dose for Each Subject

Subjects will receive 3 infusions of sipuleucel-T at approximately 2 week intervals. Each dose of sipuleucel-T contains a minimum of 50 million autologous CD54+ cells activated with recombinant fusion protein composed PAP linked to GM-CSF (PA2024).

7.4 Sipuleucel-T Treatment Compliance

Sipuleucel-T treatment compliance is evaluated by each site's clinical trial infusion personnel.

7.5 Destruction and Return of Sipuleucel-T

Clinical trial site personnel will dispose of sipuleucel-T bags and tubing according to institutional procedures for disposal of biohazardous waste that contains human blood. All sipuleucel-T packaging materials and gel packs will be disposed of according to institutional procedures.

If instructed by Dendreon to return the remaining sipuleucel-T, tubing, or both, clinical trial site personnel will place these items in the original shipping box with the original packaging materials and ship them according to Dendreon's instructions.

8.0 STUDY ASSESSMENTS AND PROCEDURES

8.1 Schedule of Events for Subjects Randomized to Sipuleucel-T

The Schedule of Events for subjects randomized to sipuleucel-T is presented in Table 1.

Table 1: Schedule of Events for Subjects Randomized to Sipuleucel-T

Item	Screening /Baseline[a]	Randomization[b]	Leukapheresis 1	Infusion 1 (Week 0)	Leukapheresis 2	Infusion 2	Leukapheresis 3	Infusion 3	Weeks 2, 4, 6, 10, 14, 26 IM Visits Post 1'st Infusion[e]	Every 6-Month Visit Post Randomization[e]	Every 12-mont Visit	Biopsy 1 & Biopsy 2	End of Active Phase Visit[n]	End of Active Phase and Beginning of Follow up Phase[o]	Every 6-Month Follow Up Visit[o]	Early Withdrawal Visit[p]
Visit Window	≤30 days prior randomization			~3 days after leukapheresis 1		~3 days after leukapheresis 2		~3 days after leukapheresis 3	± 7 days	± 14 days	± 14 days	12 to 18 & 33 to 39 months post randomization	Within 1 mo. of Biopsy 2		± 1 Month	
Informed Consent	X															
Prostate Biopsy	X[c]											X[j]				
Leukapheresis			X[s]		X		X									
Sipuleucel-T Infusion				X		X		X								
Clinical Evaluations																
Demographics	X															
Medical History	X															
Physical Examination and Vital Signs[d]	X		X		X		X						X			X
Digital Rectal Exam	X									X						
ECOG Performance Status	X															
Cardiovascular Risk Factors[q]	X															
ECG	X															
AEs and SAEs			X	X	X	X	X	X	X	X		X	X		X	X
Concomitant Medications	X		X	X	X	X	X	X	X	X		X	X			X
Prostate Cancer Treatment[h]	X		X	X	X	X	X	X	X	X		X	X		X	X
Patient Reported Outcomes[i]	X										X				X	X
Survival Status[f]										X		X	X		X	X

Item	Screening /Baseline[a]	Randomization[b]	Leukapheresis 1	Infusion 1 (Week 0)	Leukapheresis 2	Infusion 2	Leukapheresis 3	Infusion 3	Weeks 2, 4, 6, 10, 14, 26 IM Visits Post 1'st Infusion[d]	Every 6-Month Visit Post Randomization[e]	Every 12-mont Visit	Biopsy 1 & Biopsy 2	End of Active Phase Visit [n]	End of Active Phase and Beginning of Follow up Phase[o]	Every 6-Month Follow Up Visit[o]	Early Withdrawal Visit [p]
Visit Window	≤30 days prior randomization			~3 days after leukapheresis 1		~3 days after leukapheresis 2		~3 days after leukapheresis 3	± 7 days	± 14 days	± 14 days	12 to 18 & 33 to 39 months post randomization	Within 1 mo. of Biopsy 2		± 1 Month	
Laboratory Tests																
IHC and Gleason Score	X[c]											X[j]				
Viral Serology[m]	X															
Chemistry and Hematology[r]	X												X			X
PSA	X[g]									X[g]					X[t]	X
Total Testosterone	X															
Immune Monitoring Sample Collection																
100 mL sample[l]				X[k]					X[k]	X						
8.5 mL sample PAXGENE RNA				X[k]					X[k]	X						
2.0 mL sample PAXGENE DNA				X[k]												

[a] All screening/baseline procedures must occur within 30 calendar days prior to randomization, with the exception of written informed consent and diagnostic biopsy

[b] Randomization is the final event of Screening once eligibility of subject is confirmed by the PI.

[c] Pre-study biopsy(ies) is (are) not a study procedure and the first diagnosed biopsy must have been performed ≤12 months of signing ICF. The biopsy (ies) H&E and special stained slides that were used for prostate cancer diagnosis must be submitted for BICR to determine subject eligibility.

[d] Complete PE including vital signs done at the clinical site at Screening (genitourinary, skin, pulmonary, cardiovascular, neurological, gastrointestinal & musculoskeletal) and abbreviated PE per PI's discretion within 7 days prior to each leukapheresis and End of Active Phase Visit. Weight will be measured at each PE; height will be measured at Screening only.

[e] The 26-week post-first-infusion visit and first 6-month visit post randomization may occur on the same visit day and only one set of immune samples need to be collected if the visits fall on the same day.

[f] Survival status will not be obtained for subjects that are lost to follow up or withdrawn from the study.

[g] PSA should be collected prior to DRE and biopsy procedures.

[h] Any prostate cancer treatment (e.g., surgery, radiation, androgen deprivation therapy).

[i] Patient reported outcomes/Quality of life questionnaire (IPSS, Max-PC, SF-12 and EPIC-CP) should be collected every 12 months (12-, 24-, and 36-month visits) prior to any procedures.

[j] Biopsy 1 may take place between 12 months and 18 months post randomization. Biopsy 2 may take place between 33 months and 39 months post randomization.

[k] Immune monitoring sample collection time points are calculated from the date of first infusion (note: not from randomization). Samples collected on infusion days (i.e., Weeks 0, 2, 4) will be drawn prior to starting the sipuleucel-T infusion. A single PAXGENE DNA sample is only collected at Week 0.

[l] Blood draws for immune response analyses: 100mL total draw (90ml into NaHeparin Vacutainer for PBMC isolation and 10mL into no-anticoagulant vacutainer tubes for serum isolation).

[m] Viral serology consists of hepatitis panel (HBsAg, HBsAb, HBcAb, HCV antibody(Ab), if Ab+ then HCV RNA)), HIV-1, HIV-2 antibody screen, and HTLV-1, HTLV-2 antibodies

[n] End-of-Active Phase visit will take place within 30 days following Biopsy 2.

[o] Follow-up visits will start 6 months after the End-of-Active Phase visit.

[p] The early withdrawal visit must occur within 30 days of the last visit.

[q] Risk factors for cardiovascular events will include diabetes mellitus, smoking history, family history, left ventricular hypertrophy, atrial fibrillation, hypertension, myocardial infarction and other cardiovascular disease.

[r] Chemistry and/or hematology should be completed at a local lab within 7 days of leukapheresis as requested by the Apheresis center

[s] First leukapheresis will be given within 60 days of randomization

[t] PSA collected per standard of care, analyzed by local lab

Table 2: Schedule of Events for Subjects Randomized to Control

Item	Screening /Baseline[a]	Randomization[b]	3-Month Visit Post Randomization[o]	Every 6-Month Visit Post Randomization	Every 12-mont Visit	Biopsy 1 & Biopsy 2	End of Active Phase Visit[k]	End of Active Phase and Beginning of Follow up Phase[l]	Every 6-Month Follow Up Visit[l]	Early Withdrawal Visit[m]
Visit Window	≤30 days prior randomization		± 14 days	± 14 days	± 14 days	12 to 18 & 33 to 39 months post randomization	Within 1 mo. of Biopsy 2		± 1 Month	
Informed Consent	X									
Prostate Biopsy	X[c]					X[i]				
Clinical Evaluations										
Demographics	X									
Medical History	X									
Physical Examination and Vital Signs[d]	X						X			X
Digital Rectal Exam	X			X						
ECOG Performance Status	X									
Cardiovascular Risk Factors[n]	X									
ECG	X									
AEs and SAEs			X	X		X	X		X	X
Concomitant Medications	X		X	X		X	X			X
Prostate Cancer Treatment[g]	X		X	X		X	X		X	X
Patient Reported Outcomes[h]	X				X				X	X
Survival Status[e]			X	X		X	X		X	X
Laboratory Tests										
IHC and Gleason Score	X[c]					X[i]				
Viral Serology[j]	X									
Chemistry and Hematology	X						X			X
PSA	X[f]			X[f]					X[p]	X
Total Testosterone	X									

[a] All screening/baseline procedures must occur within 30 calendar days prior to randomization, with the exception of written informed consent and diagnostic biopsy
[b] Randomization is the final event of Screening once eligibility of subject is confirmed by the PI.
[c] Pre-study biopsy(ies) is (are) not a study procedure and must have been performed ≤12 months of signing ICF. The biopsy (ies) H&Eand special stained slides that were used for prostate cancer diagnosis must be submitted for BICR to determine subject eligibility.
[d] Complete PE including vital signs done at the clinical site at Screening (genitourinary, skin, pulmonary, cardiovascular, neurological, gastrointestinal & musculoskeletal) and abbreviated PE per PI's discretion at the End of Active Phase Visit. Weight will be measured at each PE; height will be measured at Screening only.
[e] Survival status will not be obtained for subjects that are lost to follow up or withdrawn from the study.
[f] PSA should be collected prior to DRE and biopsy procedures
[g] Any prostate cancer treatment (e.g., surgery, radiation, androgen deprivation therapy)
[h] Patient reported outcomes/Quality of life questionnaire (Max-PC, SF-12 EPIC-CP, and IPSS) should be collected every 12 months (12-, 24-, and 36-month visits) prior to any procedures on the specified visits.
[i] Biopsy 1 may take place between 12 months and 18 months post randomization. Biopsy 2 may take place between 33 months and 39 months post randomization.
[j] Viral serology consists of hepatitis panel (HBsAg, HBsAb, HBcAb, HCV antibody(Ab), if Ab+ then HCV RNA)), HIV-1, HIV-2 antibody screen, and HTLV-1, HTLV-2 antibodies
[k] End-of-Active Phase visit will take place within 30 days following Biopsy 2.
[l] Follow-up visits will start 6 months after the End-of-Active Phase visit.
[m] The early withdrawal visit must occur within 30 days of the last visit.
[n] Risk factors for cardiovascular events will include diabetes mellitus, smoking history, family history, left ventricular hypertrophy, atrial fibrillation, hypertension, myocardial infarction and other cardiovascular disease.
[o] 3-month visit post randomization may be conducted in the office or via phone.
[p] PSA collected per standard of care, analyzed by local lab

8.2 Informed Consent

Informed consent will be obtained as described in Section1.4.

8.3 Screening

All subjects must sign an ICF prior to the conduct of any study-related procedures. A screening number will be assigned for each subject. Screening procedures will be performed up to 30 days prior to randomization to allow sufficient time for blood chemistries and submission of all original stained pathology slides along with local pathology report for BICR to determine ISUP Grade Group for inclusion criteria and randomization. All subject information should be redacted from the local pathology reports and slides. Local pathology reports and slides will be identified only by subject screening number. If a subject has more than one biopsy following their prostate cancer diagnosis, slides from each subsequent biopsy will be sent for BICR. The central pathologist's report will determine whether the subject meets the prostate cancer eligibility criteria (Section 6.0). All slides will be returned to the clinical trial site. In the case of multiple biopsies, the biopsy with the highest ISUP Grade Group will be used as baseline.

See the complete list of inclusion and exclusion criteria (Section 6.0) and the Schedule of Events (Table 1 and Table 2) for study details.

Subjects who do not meet all inclusion criteria and/or who meet one or more exclusion criteria may be rescreened. Rescreening is at the discretion of the investigator, but requires sponsor approval in writing. Subjects who are to be rescreened must sign a new ICF prior to rescreening. Rescreened subjects who had their initial screening performed within 30 days of randomization may use the initial screening laboratory results. Rescreened subjects may use the initial ISUP Grade Group determined by BICR if no additional biopsy has been administered. Rescreening and subsequent randomization activities must be conducted in accordance with all protocol-defined windows and timelines.

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

8.4 Randomization

Eligible subjects will be randomized to the sipuleucel-T arm or control arms in a 2:1 ratio based on a predetermined, computer-generated randomization schedule. The randomization will be balanced by using block randomization.

Stratification will be based on:

- ISUP Grade Group 1 or 2
- Number biopsies 1 or >1 (≤12 months of Screening)

Randomization will take place across all clinical trial sites using an Interactive Response Technology (IRT). The IRT will assign a unique code, which will dictate the assignment to either sipuleucel-T arm or control arm. The requestor must use his or her own user identification and personal identification number when contacting the IRT, and will then give the relevant subject details to uniquely identify the subject.

8.5 Demographics and Medical History

Demographic information, including birth date, race, and ethnicity will be recorded.

Medical history will include date of prostate cancer diagnosis, ISUP Grade Group and prostate biopsy history. Significant historic (within the previous 5 years) and current medical conditions or illnesses, allergies to medications, and surgical interventions occurring prior to informed consent will be recorded. Medical history will include the subject's serum PSA values and vaccinations in the 2 years prior to signing informed consent.

8.6 Clinical Assessments

8.6.1 Physical Examination and Vital Signs

PEs must be conducted by an appropriately qualified investigator listed on Form FDA 1572.

Complete PEs will be performed at Screening and include a review of body systems (genitourinary, skin, pulmonary, cardiovascular, neurological, gastrointestinal and musculoskeletal. Review of additional body systems will be at the discretion of the investigator.

For the sipuleucel-T arm abbreviated PEs will be performed on the day of leukapheresis or within 7 days prior to leukapheresis. For both sipuleucel-T and control arms abbreviated PEs will be performed at the End of Active Phase Visit or at the Early Withdrawal Visit. Weight will be measured at each PE; height will be measured at Screening only.

Vital signs (respiration rate, temperature, heart rate, and blood pressure) will be measured at the time points noted in Schedule of Events (Table 1 or Table 2).

8.6.2 Digital Rectal Exam

DRE will be performed at screening and each 6-month visit in the Active Phase and should be performed after blood draw for PSA.

8.6.3 Electrocardiograms

A 12-lead ECG will be recorded at Screening. Abnormalities noted at Screening will be included in the medical history.

8.6.4 Eastern Cooperative Oncology Group Performance Status

ECOG performance status (Appendix 1) will be assessed at Screening. The assessment must be conducted by an appropriately qualified investigator listed on the Form FDA 1572 and noted on the delegation log.

8.6.5 Cardiovascular Risk Factors

Risk factors for cardiovascular events will be recorded at Screening and will include diabetes mellitus, smoking history, family history, left ventricular hypertrophy, atrial fibrillation, hypertension, myocardial infraction, and other cardiovascular disease.

8.6.6 Multiparametric Magnetic Resonance Imaging (mpMRI) Imaging Study

When available, existing mpMRI prostate imaging studies performed prior to randomization and as part of the original prostate cancer diagnosis or subsequent prostate biopsies will be documented in the eCRF. Comparative mpMRI prostate imaging studies performed on study will be captured in the eCRF.

8.7 Patient Reported Outcomes

PRO data will be collected to evaluate health-related quality of life for men on AS and the impact of any subsequent therapy for prostate cancer. Four instruments SF-12 (Appendix 2), MAX-PC (Appendix 3), EPIC-CP (Appendix 4), and the IPSS (Appendix 5) will be administered at Screening, annually during the Active Phase at 12-, 24-, and 36-month visits, and every 6 months in the Follow up Phase or Early Withdrawal Visit. SF-12 evaluates the general quality of life, MAX-PC evaluates a subject's anxiety related to prostate cancer diagnosis, EPIC-CP measures quality of life issues in patients with prostate cancer, and the IPSS evaluates patient's urinary voiding symptoms. PROs should be administered prior to any procedures or measurements. The clinical site staff must review the completed PRO's with the subject prior to leaving the facility to ensure that PROs have been completed correctly.

8.8 Adverse Events and Serious Adverse Events

AE and SAE assessments will be performed in conjunction with visits as indicated in Schedule of Events (Table 1 and Table 2) and as needed throughout the study. All AEs and SAEs will be recorded in the subject's medical record and on the eCRF. In addition all SAEs will be reported on the sponsor's SAE report form.

See Section 9.1 for information regarding AE and Section 9.2 for information regarding SAEs.

8.9 Concomitant Medications and Therapies

All concomitant medications that are ongoing at informed consent or administered during the Active Phase will be recorded at each scheduled and unscheduled study visit in the subject's medical record and eCRF. See Section 6.7 and Section 6.8 for restricted therapies. Only

prostate cancer treatments (e.g., surgery, radiation, androgen deprivation therapy) administered during the Follow-up Phase visits will be recorded in the subject's medical record and eCRF.

8.10 Clinical Laboratory Tests

Clinical laboratory test samples will be collected at the time points noted in the Schedule of Events (Table 1 and Table 2). Samples will be tested for the parameters presented in Table 3. All clinical laboratory tests will be performed by a central laboratory, and the results will be reported to the clinical trial site.

Table 3: Laboratory Tests

HEMATOLOGY	CLINICAL CHEMISTRY
Hemoglobin (HgB)	Total bilirubin
Hematocrit	Alkaline phosphatase
Red blood cell count (RBC)	Lactic Dehydrogenase (LDH)
White blood cell count (WBC)	Alanine aminotransferase (ALT/SGPT)
Absolute neutrophil count (ANC)	Aspartate aminotransferase (AST/SGOT)
Lymphocyte count	Blood urea nitrogen (BUN)
Monocyte count	Serum creatinine
Eosinophil count	Calcium
Basophil count	Magnesium
Platelet count	Glucose
OTHER BLOOD TESTS	Albumin
Total testosterone	Total Protein
Prostate-specific antigen (PSA)	Sodium
VIRAL SEROLOGY	Potassium
Human Immunodeficiency Virus (HIV-1 and HIV-2)	Bicarbonate
Hepatitis panel (HBsAg, HBsAb, HBcAb, HCV antibody(Ab), if Ab+ then HCV RNA))	Chloride
Human T-Lymphotropic Virus (HTLV-1, HTLV-2)	Phosphorus

8.11 Histopathology Assessment

During the Active Phase, subjects will have all H&E and special stained slides and local pathology reports from Biopsy 1 and Biopsy 2, as well as any unscheduled biopsies, assessed for histopathologic grading by BICR. Slides from each biopsy will be considered as a group to determine the ISUP Grade Group as opposed to any single slide. All subject information should be redacted from the local pathology reports and slides. Local pathology reports and slides will be identified only by study subject number. All slides will be returned to the clinical trial site.

Subjects on the Active Phase undergoing a radical prostatectomy will submit H&E and special stained slides from prostate slices for BICR as described above. These will be compared to the ISUP Grade Group determined from previous biopsy. FFPE tissue blocks from the radical prostatectomy as requested by central pathology will be submitted for IHC.

Subjects with an ISUP Grade Group upgrade and who remain on AS (i.e., do not undergo prostate cancer therapy) will remain in the Active Phase and continue per the Schedule of Events (Table 1 and Table 2).

8.12 Immunohistochemistry Evaluations

Post randomization, specific FFPE tissue blocks from biopsies or surgery will be requested by central pathology from their BICR that represents areas of cancer and benign prostate tissue identified on H&E and special stained slides. All subject information should be redacted from the FFPE blocks, and FFPE blocks should be identified only by study subject number. These blocks will be freshly cut by the central pathology for IHC to assess infiltration and classification of lymphocytes (e.g., CD3, CD4, CD8, FoxP3, CD56, Ki67, CD279, MECA-79) to prostate cancer tissue. The geographic distribution of T cell phenotypes will be described relative to the tumor (central, peripheral, adjacent, or benign tissue localization). All FFPE blocks will be returned to the clinical trial site.

8.13 Sipuleucel-T Immune Monitoring Assessments

Blood samples for immune monitoring will be collected at the time points noted in the Schedule of Events (Table 1) for subjects randomized to the sipuleucel-T arm.

Immune monitoring assessments will include proliferation assays to evaluate PA2024- and PAP-specific T cell responses, IFN-γ ELISPOT assays to assess the number of PA2024- and PAP-specific T cells, and enzyme-linked immunosorbent assay (ELISA) to assess humoral response to PA2024 and PAP. Fluorescent immunoassays will be used to determine the number and activation status of subtypes of T cells, B cells, and NK cells, and the levels and types of cytokines.

8.13.1 Sipuleucel-T Product Parameters

Prior to infusion, samples from pre and post-culture sipuleucel-T are used to assess product parameters as part of the sipuleucel-T manufacturing process. Sipuleucel-T product parameters include total nucleated cell (TNC) count, APC count, and APC activation.

8.13.2 Sipuleucel-T Product Characterization

Samples of final product will be used to characterize sipuleucel-T utilizing flow cytometry, protein array, spectral analyses, ELISA, and Luminex assays to assess the immune response. Tests may include assessment of the number and activation status of subtypes of T cells, B cells, and NK cells, and the levels and types of cytokines produced during the manufacture of sipuleucel-T.

8.13.3 Additional Optional Research (AOR)

At the time of informed consent, subjects will be given the opportunity to consent to participate in AOR. Subjects who consent to AOR agree to allow sponsor or designee to retain their

samples (obtained from blood collection for immune monitoring, PAXGENE RNA and DNA, and sipuleucel-T product parameters and characterization, during manufacture) indefinitely and to use them for other testing. For subjects who consent to AOR, no additional blood collections will be required beyond those already being collected as part of the study.

AOR may include genetic testing, and retained samples may be sent to outside laboratories for testing.

Samples retained for AOR will be used for research only, will not be sold, and will not be identified using subject names or other personal identifiers.

FFPE tissue blocks from biopsies used for screening and on study biopsies or radical prostatectomy may be requested by the sponsor for genomic analysis of prostate cancer progression risk.

8.13.4 Sample Retention

Blood or serum samples obtained for clinical laboratory testing from all subjects will be retained by the central laboratory for up to 7 days and will then be destroyed.

Blood or serum samples obtained for immune monitoring, or manufacturing process samples for sipuleucel-T product parameters and characterization will be retained for up to 5 years following sponsor's completion of the trial and will then be destroyed. Subjects who consent to AOR agree for the sponsor to retain the samples indefinitely.

Samples obtained or used for immune monitoring and sipuleucel-T product parameters and characterization from subjects who provide consent for AOR may be retained indefinitely.

FFPE tissue blocks obtained for IHC and genomic analysis will be returned to the sites.

9.0 SAFETY

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. Safety reporting for this trial will be conducted in accordance with 21 CFR 312.32 as amended by the Final Rule published September 29, 2010 and detailed in the Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies (December 2012). Sponsor will be the final arbiter, should a difference of opinion exist regarding the nature, seriousness, severity, or relatedness of AEs.

9.1 Adverse Events

9.1.1 Definition of Adverse Event

An AE is defined as any untoward medical occurrence in a subject while participating in a study that does not necessarily have a causal relationship with sipuleucel-T. An AE can, therefore, be any unfavorable and unintended sign (e.g., abnormal laboratory finding), symptom, or

disease temporally associated with sipuleucel-T, whether or not considered related to sipuleucel-T. AEs 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.

9.1.2 Categories for Ranking Severity of Adverse Events

The most current version of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) will be used to score AE severity by grades. In general, the following 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 be expected to result in death unless immediate medical intervention is undertaken.
Fatal (grade 5):	The AE results in death.

9.1.3 Relationship of Adverse Events to Sipuleucel-T

The following categories will be used to determine relationship of AEs to sipuleucel-T:

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 sipuleucel-T, 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 sipuleucel-T and could not readily have been produced by the subject's clinical state, environmental factors, or other modes of therapy or concomitant medications administered to the subject.

9.1.4 Recording and Reporting Adverse Events

All AEs and SAEs in the sipuleucel-T arm and control arm will be collected from randomization through the subject's last study visit. AEs and SAEs will be reported and recorded in the subject's medical record and entered on their eCRF.

All AEs and SAEs reported in either the sipuleucel-T or control arms will be followed by the investigator until resolution, return to baseline, or the investigator determines that no further improvement is expected until study completion. The start and stop dates, description, seriousness, toxicity, relationship to study treatment, and outcome will be recorded.

9.2 Serious Adverse Events

9.2.1 Definition of Serious Adverse Event

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 an 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.

9.2.2 Recording and Reporting of Serious Adverse Events

All SAEs in the sipuleucel-T arm and control arm from randomization through the subject's last study visit will be reported on sponsor's SAE Report Form.

All SAEs reported in both arms will be followed by the investigator until resolution, return to baseline, or the investigator determines that no further improvement is expected until study completion.

SAEs must be reported to sponsor or designee within 24 hours of the clinical trial site's awareness of the events by completing the sponsor's SAE Report Form if they meet the criteria described in Section 9.2.1. If access to the SAE Report Form is unavailable for any reason, the SAE information must be reported to sponsor or designee within 24 hours by email or facsimile and a completed written report using sponsor's SAE Report form within 3 business days to:

Dendreon Pharmaceuticals LLC

Attention: DrugSafety@dendreon.com

Significant new information regarding each SAE must be reported to sponsor or designee by recording the information on the SAE Report Form within 24 hours of the clinical trial site's awareness of the new information and reported as noted above.

9.2.3 Death Reports

Deaths that occur during the study will be reported as SAEs and will be recorded in the subject's medical record, sponsor's SAE Report Form and on the eCRF.

9.2.4 Expedited Reporting Requirements

Sponsor will notify the appropriate regulatory authorities and all participating Principal Investigators of any AE that is serious, unexpected and considered to be at least possibly related to sipuleucel-T. Such notification will be provided within 15 calendar days after Sponsor or designee's initial receipt of the information. If such an event is fatal or life-threatening, the appropriate regulatory authorities will be notified no later than 7 calendar days after Sponsor or designee's initial receipt of the information.

Serious adverse events that are expected, such as disease progression, will not be reported by sponsor on an expedited basis. See the sipuleucel-T Investigator's Brochure for additional information regarding expected SAEs.

The Principal Investigator is responsible for notifying the relevant IRB of any SAE that occurs in a subject participating at their clinical trial site or any IND Safety Reports issued by sponsor, unless otherwise instructed by relevant IRB policy.

9.3 Laboratory Test Result Abnormalities

The following laboratory abnormalities will be considered AEs and recorded in the subject's medical record and on the eCRF:

- 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 discontinuation or interruption of sipuleucel-T
- Any result that requires therapeutic intervention or a change in subject management

Laboratory abnormalities that do not meet the above conditions will not be recorded on the eCRF.

10.0 STATISTICAL CONSIDERATIONS

The Phase 3, open-label study is designed to assess the effects of sipuleucel-T in subjects on AS. Subjects will be randomized 2:1 to either a sipuleucel-T arm (investigational arm) or a control arm, stratified by the ISUP Grade Group 1 or 2 and the number of biopsies showing the presence of disease prior to registration. Data will be analyzed by arm under the intent-to-treat (ITT) principle. Generally statistical tests will be performed at the 2-sided 0.05 significance level unless otherwise noted.

The phrases 'statistical analysis' or 'analysis' will be used to mean inferential analysis (such as performing tests of significance, reporting p-values and confidence intervals). When no inferential analysis will be performed, the phrases 'descriptive analysis' or 'descriptive statistics' will be used (for instance, producing summary tables of means, standard deviations, percentages of responders).

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Details will be provided in the Statistical Analysis Plan (SAP).

10.1 Sample Size Considerations

The primary endpoint will analyze approximately 450 subjects randomized (2:1 sipuleucel-T versus control arm), and for each subject, is dichotomous with success defined as having been observed to be free of histopathologic upgrade after 36 months of follow-up. Based on data available, it is estimated that the proportion of histopathologic upgrading by 36 months following randomization for control arm subjects will be approximately 0.30. While there is no prior information on treatment response to sipuleucel-T in early stage disease available, a meaningful hypothesized reduction in this proportion is a reduction by 0.14, giving a projected outcome proportion of upgrading in the sipuleucel-T arm of 0.16. The null hypothesis of both arms having a proportion of 0.70 (= 1- 0.3) being free from upgrading at 36 months versus the

specific alternative hypothesis of a sipuleucel-T arm outcome of 0.84 (= 1- 0.16). The odds ratio associated with the specific alternative hypothesis is 2.25 (sipuleucel-T arm odds over control arm odds). Based on an overall 1-sided alpha of 0.025 approximately 300 subjects in the sipuleucel-T arm and 150 subjects in the control arm will provide 90% power to demonstrate the superiority of sipuleucel-T to control.

10.2 Analysis Populations

The Safety Analysis Population is defined as all randomized patients; the Sipuleucel-T safety population must have begun the treatment process.

The intent-to-treat (ITT) population is defined as all randomized subjects.

The Per Protocol (PP) population is defined as the subset of patients in the ITT population who have completed all assessment per the protocol.

10.3 Efficacy Analysis

The phrases ‘statistical analysis’ or ‘analysis’ will be used to mean inferential analysis (such as performing tests of significance, reporting p-values and confidence intervals). When no inferential analysis will be performed, the phrases ‘descriptive analysis’ or ‘descriptive statistics’ will be used (for instance, producing summary tables of means, standard deviations, percentages of responders). All efficacy analyses will be conducted on the ITT population and the per protocol population.

Unless otherwise specified, the statistical tests are based on the superiority hypothesis using a one-sided p-value of 0.025 (equivalent to two-sided 0.05 with a result in the hypothesized direction). The final analysis will be performed after all subjects have completed the 36 month biopsy, or have histopathologic upgrade or have withdrawn from the study.

10.4 Interim Analysis

No interim analysis is proposed.

10.5 Analysis of Study Endpoints

10.5.1 Primary Endpoint

The primary endpoint is the proportion of subjects without a histopathologic upgrade over the 36-months following randomization and will be summarized by study arm. The primary endpoint for each subject is dichotomous with success defined as having been observed to be free of histopathologic upgrade at Biopsy 2 33 to 39 months after randomization. Histopathologic upgrading occurs when a subject with ISUP Grade Group 1 prostate cancer, at randomization, is upgraded to Grade Group 2 or higher, or a subject with ISUP Grade Group 2 prostate cancer, at randomization, is upgraded to Grade 3 or higher as determined by BICR, at any post-randomization biopsy. Histopathologic status is determined by biopsy and will be assessed at the scheduled biopsy or at any biopsy that is taken during radical-prostatectomy or

other time-point. Subjects upgrading before 36 months, or those found as upstaged at Biopsy 2, or those not observed at 36 months (i.e., do not complete Biopsy 2 prior to 39 months post randomization) will be regarded as failures in the primary analysis.

The primary analysis null hypothesis, H0: $\Omega \leq 1$, versus the alternative hypothesis, HA: $\Omega > 1$; where Ω is the odds of success in the sipuleucel-T arm over the odds of success in the control arm. The Cochran-Mantel-Haenszel (CMH) test, stratified by ISUP Grade Group 1 or 2 and the number of biopsies showing the presence of disease prior to registration will be used to estimate the odds ratio, and will be computed using exact methods based on Monte Carlo computations due to the potential for small frequencies.

10.5.2 Secondary Endpoints

The subsequent prostate cancer treatment, if any, for each subject will be determined. The category of subsequent prostate cancer treatment will be identified (e.g., surgery, radiation, androgen deprivation therapy). Subjects initiating alternative intervention will be regarded as sipuleucel-T treatment failures. These data will be summarized descriptively and compared between study arms using the Cochran-Mantel-Haenszel test.

Quality of life data will be summarized descriptively and compared between study treatment arms and in the aggregate within the efficacy population.

Safety data will be summarized descriptively by study treatment arms and in the aggregate within the safety population.

10.5.3 Exploratory Endpoints

Immune response will be assessed at each specified time-point. Immune response variables will be evaluated to determine if there is a correlation between the measures of immune response and upgrade or other changes to the ISUP group grade of the subject's prostate cancer.

Subjects undergoing a radical prostatectomy will have the biopsy sample evaluated for histological status of the prostate cancer. Histopathologic change will be defined as any change in ISUP grade at baseline to an upgrade, no change in, or down-grade to a their ISUP baseline grade group designation, or to a status indicating no prostate cancer disease identified. These data will be summarized descriptively and compared between study arms.

Biopsy results will be assessed to determine the rate of negative biopsy results. This data will be summarized descriptively and compared between study arms.

PSA velocity will be calculated as the slope of the simple linear regression of the natural log of PSA versus time.

10.5.4 Biomarker Analysis

The association of biomarkers with clinical response endpoints or survival may be assessed using appropriate statistical methods (e.g., analysis of variance [ANOVA], categorical or

survival models) depending on the endpoints. Other clinical covariates (such as baseline tumor characteristics and subject demographics) may also be included in the model. Association of biomarkers with clinical response or relevant time-to-event endpoints will also be explored in the overall population. Results of these exploratory analyses will be presented in separate technical reports.

10.5.5 Safety

The safety parameters to be analyzed are the incidence, intensity, and type of AEs, vital signs, clinical laboratory results, and limited physical examinations (abnormalities will be recorded as AEs (Section 9.3). Analysis of the safety parameters will be conducted on the safety population.

10.5.5.1 Adverse Events

AEs will be summarized and listed using the Medical Dictionary for Regulatory Activities (MedDRA version 18.0 or later) by preferred term within each body system. Tables to be produced will include the number and incidence of the following:

- Incidence within system organ class
- Incidence by decreasing frequency
- Incidence by NCI CTCAE (most current version) severity grade, by decreasing frequency
- Incidence within 1 day of infusion
- Incidence of SAEs
- Incidence of AEs that resulted in premature discontinuation of study

AEs 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.

10.5.5.2 Clinical Laboratory Data

Clinical laboratory test results will be summarized by type of laboratory test. For continuous measurements, descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. The number and percentage of subjects with abnormal values will be summarized. The number and percentage of subjects with parameters with NCI-CTCAE toxicity Grade of ≥3 will be summarized. Shift in toxicity grade from baseline to the worst grade experienced by the subject during the study will be provided.

10.5.5.3 Other Clinical Assessments

Descriptive statistics of blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point. Descriptive statistics of other vital signs

(body temperature, heart rate, respiratory rate) at baseline will also be summarized. The number and percentage of subjects with values beyond clinically important limits will be summarized.

Abnormal findings in physical examination will be recorded and summarized as AEs. Weight will be summarized and DRE results will be provided in a listing.

10.5.6 Other

10.5.6.1 Demographics and Baseline Characteristics

Demographic information and baseline disease characteristics will be summarized descriptively for the primary analysis population and the treated and safety populations.

10.5.6.2 Subject Disposition

The following subject disposition information will be summarized:

- Number of subjects in the primary analysis population
- Number of subjects in the treated population
- Number of subjects in the safety population
- Number of subjects who prematurely discontinued the study and the associated reasons for early termination

10.5.6.3 Sipuleucel-T Administration

The following leukapheresis and infusion information will be summarized for all registered subjects:

- 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 leukapheresis
- Number of subjects who receive a total of 3 leukapheresis and 3 infusions

10.5.6.4 Sipuleucel-T Product Parameters

Sipuleucel-T product parameters (TNC count, APC count, and APC activation) will be summarized by Infusion 1, 2, 3, cumulative through Infusion 2, and cumulative through Infusion 3.

10.5.6.5 Concomitant Medications and Therapies

Concomitant medications will be coded using the World Health Organization dictionary (WHODRUG).

All concomitant medications will be summarized by anatomical-therapeutic-chemical classification (ATC) text and preferred term. Separate summaries will be provided for medications ongoing at the time of informed consent and for medications started after informed consent.

11.0 STUDY MANAGEMENT

11.1 Study Materials

Sponsor or designee will provide an approved protocol and any required amendments or administrative letters, the current Investigator's Brochure, and the eCRF. Dendreon or designee will also provide leukapheresis services at a Dendreon-qualified leukapheresis center and all applicable study-specific training materials and reference binders. Sponsor or designee will additionally provide materials needed for the collection and shipment of laboratory samples, including samples for immune monitoring.

The clinical trial site will provide all other supplies required to conduct the study at the clinical trial site.

11.2 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 or designee, IRBs, FDA, or other regulatory authorities at any time, and should consist of the following:

- Copies of completed eCRFs
- Subject files, containing supporting source documentation from the subject's medical record, including clinical laboratory data, pathology reports, and the original signed ICF (including any updated ICFs requiring re-consenting)
- Essential documents, as defined in ICH E6 Guideline for GCP
- Drug accountability files, containing a complete account of the receipt and disposition of all sipuleucel-T infusions

The Principal Investigator shall retain records 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 the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

11.3 Protocol Compliance

To ensure accurate interpretation and implementation of the study, the protocol will be carefully reviewed by the Principal Investigator and the clinical trial site personnel prior to study initiation.

Any non-adherence to the protocol, FDA regulations, or GCP will be considered a protocol deviation, and will be discussed during a monitoring visit and documented via a visit follow-up letter. The Principal Investigator will be responsible for reporting protocol deviations to the IRB per the IRB's reporting requirements.

A protocol exception is a specific type of protocol deviation wherein a subject does not meet eligibility requirements for the study, but a waiver allowing the subject to enter the study is prospectively granted by sponsor. Protocol exceptions are rarely considered, and are granted only when a subject's participation will not confound analysis or interpretation of safety data.

11.4 Monitoring

A sponsor monitor or designee will visit the clinical trial site periodically to monitor adherence to the protocol, adherence to applicable FDA regulations, adherence to ICH E6 Guideline for GCP, and the maintenance of adequate and accurate records. Electronic case report forms will be reviewed to ensure that key safety and efficacy data are reported as specified by the protocol. The sponsor monitor or designee must be permitted to access subjects' complete medical records, laboratory data, and other source documentation as needed to appropriately monitor the trial.

In addition to monitoring visits to the site, site management contacts (via phone/email) will be scheduled with the site to review study-related topics, such as, enrollment status, study staff training/turnover, safety reporting, data entry and query resolution, regulatory documentation status, study materials/expiration status, and principal investigator oversight. Frequency of these site contacts varies depending on phase of the study (approximately weekly during enrollment & closeout, and monthly during maintenance).

11.5 Independent Data Monitoring Committee

An independent data monitoring committee (IDMC) will be established to provide safety oversight for this study.

The primary role of the IDMC will be to monitor ongoing safety data, provide recommendations to sponsor executive management to protect the safety of study subjects. The IDMC members will be required to attend meetings on a regular basis. The IDMC will be completely independent from sponsor and study personnel. As part of the ongoing safety monitoring activities, the IDMC will have access to comparative results of safety and efficacy data (if necessary), aggregated by study arm.

The IDMC review of safety data will be conducted after the first 30 subjects have completed sipuleucel-T treatment. Safety reviews will then be conducted approximately every 6 months during subject enrollment period and then annually until the last subject completes Biopsy 2. Study enrollment will not be suspended during IDMC review periods.

11.6 Quality Assurance

A sponsor Quality Assurance auditor or designee may arrange and conduct visits to the clinical trial site to audit the performance of the study and the study documents originating at the site. The Principal Investigator will be informed of the outcome of audits.

In addition, inspections by FDA, other regulatory authorities, or the IRB are possible at any time. The Principal Investigator must inform sponsor of any such inspection immediately.

The clinical trial site must provide direct access to source documentation and subjects' medical records for audits and inspections.

11.7 Steering Committee

The Steering Committee will be comprised of independent experts in the treatment of prostate cancer. The Steering Committee will consult and advise regarding study design, protocol development and amendments, data analysis and interpretation, and scientific publications.

11.8 Disclosure of Data and Publication

Publications and presentations proposed by clinical trial site personnel and/or principal investigator will be furnished to sponsor for review and comment pursuant to the terms of the clinical study agreement between the clinical trial site and sponsor.

12.0 REFERENCES

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APPENDIX 1: EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

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: SHORT FORM-12 HEALTH SURVEY (SF-12)

SF-12 Health Survey

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. **Answer each question by choosing just one answer**. If you are unsure how to answer a question, please give the best answer you can.

1. **In general, would you say your health is:**

☐1 Excellent ☐2 Very good ☐3 Good ☐4 Fair ☐5 Poor

The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	YES, limited a lot	YES, limited a little	NO, not limited at all
2. Moderate activities such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.	☐1	☐2	☐3
3. Climbing several flights of stairs.	☐1	☐2	☐3

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	YES	NO
4. Accomplished less than you would like.	☐1	☐2
5. Were limited in the kind of work or other activities.	☐1	☐2

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	YES	NO
6. Accomplished less than you would like.	☐1	☐2
7. Did work or activities less carefully than usual.	☐1	☐2

8. **During the past 4 weeks, how much did pain interfere with your normal work (including work outside the home and housework)?**

☐1 Not at all ☐2 A little bit ☐3 Moderately ☐4 Quite a bit ☐5 Extremely

These questions are about how you have been feeling during the past 4 weeks.
For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks…

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
9. Have you felt calm & peaceful?	☐1	☐2	☐3	☐4	☐5	☐6
10. Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5	☐6
11. Have you felt down-hearted and blue?	☐1	☐2	☐3	☐4	☐5	☐6

12. **During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?**

☐1 All of the time ☐2 Most of the time ☐3 Some of the time ☐4 A little of the time ☐5 None of the time

Patient name: Date: PCS: MCS:

Visit type (circle one)
Preop 6 week 3 month 6 month 12 month 24 month Other:_____

APPENDIX 3: MEMORIAL ANXIETY SCALE FOR PROSTATE CANCER (MAX-PC)

The Modified 18-Item Memorial Anxiety Scale for Prostate Cancer

YOUR FEELINGS ABOUT PROSTATE CANCER AND PROSTATE SPECIFIC ANTIGEN TESTS
We would like to better understand how patients cope with aspects of their treatment for prostate cancer and the medical tests frequently involved in their care.

I. Below is a list of comments made by men about prostate cancer. Please indicate by circling the number next to each item how frequently these comments were true for you *during the past week;* not at all, rarely, sometimes, often.

	Not at all	Rarely	Sometimes	Often
1. Any reference to prostate cancer brought up strong feelings in me.	0	1	2	3
2. Even though it's a good idea, I found that getting a PSA test scared me.	0	1	2	3
3. Whenever I heard about a friend or public figure with prostate cancer, I got more anxious about my having prostate cancer.	0	1	2	3
4. When I thought about having a PSA test, I got more anxious about my having prostate cancer.	0	1	2	3
5. Other things kept making me think about prostate cancer.	0	1	2	3
6. I felt kind of numb when I thought about prostate cancer.	0	1	2	3
7. I thought about prostate cancer even though I didn't mean to.	0	1	2	3
8. I had a lot of feelings about prostate cancer, but I didn't want to deal with them.	0	1	2	3
9. I had more trouble falling asleep because I couldn't get thoughts of prostate cancer out of my mind.	0	1	2	3
10. I was afraid that the results from my PSA test would show that my disease was getting worse.	0	1	2	3
11. Just hearing the words "prostate cancer" scared me.	0	1	2	3

II. For the next three questions, please indicate how frequently these situations have *EVER* been true for you.

	Not at all	Rarely	Sometimes	Often
12. I have been so anxious about my PSA test that I have thought about delaying it.	0	1	2	3
13. I have been so worried about my PSA test result that I have thought about asking my doctor to repeat it.	0	1	2	3
14. I have been so concerned about my PSA test result that I have thought about having the test repeated at another lab to make sure they were accurate.	0	1	2	3

III. Listed below are a number of statements concerning a person's beliefs about their own health. In thinking about the *past week*, please indicate how much you agree or disagree with each statement: strongly agree, agree, disagree, or strongly disagree. Please circle the number of your answer.

	Strongly agree	Agree	Disagree	Strongly disagree
15. Because cancer is unpredictable, I feel I cannot plan for the future.	0	1	2	3
16. My fear of having my cancer getting worse gets in the way of my enjoying life.	0	1	2	3
17. I am afraid of my cancer getting worse.	0	1	2	3
18. I am more nervous since I was diagnosed with prostate cancer	0	1	2	3

PSA: prostate specific antigen.

APPENDIX 4: EXPANDED PROSTATE CANCER INDEX COMPOSITE FOR CLINICAL PRACTICE (EPIC-CP)

Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP)
Prostate Cancer Quality of Life (QOL)

Patient Name:_____ Date of Birth: _____

Physician: _____ Date of Visit: _____

Patients: Please answer the following questions by circling the appropriate answer. All questions are about your health and symptoms in the **LAST FOUR WEEKS.**

Select ONE answer for each question:

1. Overall, how much of a problem has your urinary function been for you?				
No Problem	Very small problem	Small problem	Moderate problem	Big problem

2. Which of the following best describes your urinary control?				
0-Total control	1-Occasional dribbling	2-Frequent dribbling	4- No urinary control	
3. How many pads or adult diapers per day have you been using for urinary leakage?				
0-None	1-One pad per Day	2-Two pads per Day	4- Three or more pads	
4. How big a problem, if any has urinary dripping or leakage been for you?				
0-No problem	1-Very small problem	2-Small problem	3-Moderate problem	4-Big problem
***CLINICIANS**: Add the answers from questions **2-4** to calculate the **Urinary Incontinence Symptom Score** (out of 12)*				

5. How big a problem, if any, has each of the following been for you?						
	No problem	Very small problem	Small problem	Moderate problem	Big problem	
a. Pain or burning with urination	0	1	2	3	4	
b. Weak urine stream/incomplete bladder emptying	0	1	2	3	4	
c. Need to urinate frequently	0	1	2	3	4	
***CLINICIANS**: **ADD** the answers from questions **5a-5c** to calculate the **Urinary Irritation/Obstructive Symptom Score** (out of 12)*						

6. How big a problem, if any, has each of the following been for you?						
	No problem	Very small problem	Small problem	Moderate problem	Big problem	
a. Rectal pain or urgency of bowel movements	0	1	2	3	4	
b. Increased frequency of your bowel movements	0	1	2	3	4	
c. Overall problems with your bowel movements	0	1	2	3	4	
***CLINICIANS**: **ADD** the answers from questions **6a-6c** to calculate the **Bowel Symptom Score** (out of 12)*						

7. How do you rate your ability to reach orgasm (climax)?				
0- Very good	1-Good	2-Fair	3-Poor	4-Very poor to none

8. How would you describe the usual quality of your erections?			
0- Firm enough for intercourse	1-firm enough for masturbation and foreplay	2-Not firm enough for any sexual activity	4-None at all

9. Overall, how much of a problem has your sexual function or lack of sexual function been for you?				
0-No problem	1-Very small problem	2-Small problem	3-Moderate problem	4-Big problem

10. How big a problem, if any, has each of the following been for you?						
	No problem	Very small problem	Small problem	Moderate problem	Big problem	
a. Hot flashes or breast tenderness/enlargement	0	1	2	3	4	
b. Feeling depressed	0	1	2	3	4	
c. Lack of energy	0	1	2	3	4	
***CLINICIANS**: **ADD** the answers from question s**10a-10c** to calculate the **Vitality/Hormonal Symptom Score**(out of 12)*						

***CLINICIANS**: **ADD** the five domain summary scores to calculate the Overall Prostate Cancer QOL Score (out of 60)*	

APPENDIX 5: THE INTERNATION PROSTATE SYMPTOM SCORE (I-PSS)

International Prostate Symptom Score (I-PSS)

Patient Name: _____ **Date of birth:** _____ **Date completed** _____

In the past month:	Not at All	Less than 1 in 5 Times	Less than Half the Time	About Half the Time	More than Half the Time	Almost Always	Your score
1. Incomplete Emptying How often have you had the sensation of not emptying your bladder?	0	1	2	3	4	5	
2. Frequency How often have you had to urinate less than every two hours?	0	1	2	3	4	5	
3. Intermittency How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency How often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Weak Stream How often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Straining How often have you had to strain to start urination?	0	1	2	3	4	5	
	None	**1 Time**	**2 Times**	**3 Times**	**4 Times**	**5 Times**	
7. Nocturia How many times did you typically get up at night to urinate?	0	1	2	3	4	5	
Total I-PSS Score							

Score: 1-7: *Mild* 8-19: *Moderate* 20-35: *Severe*

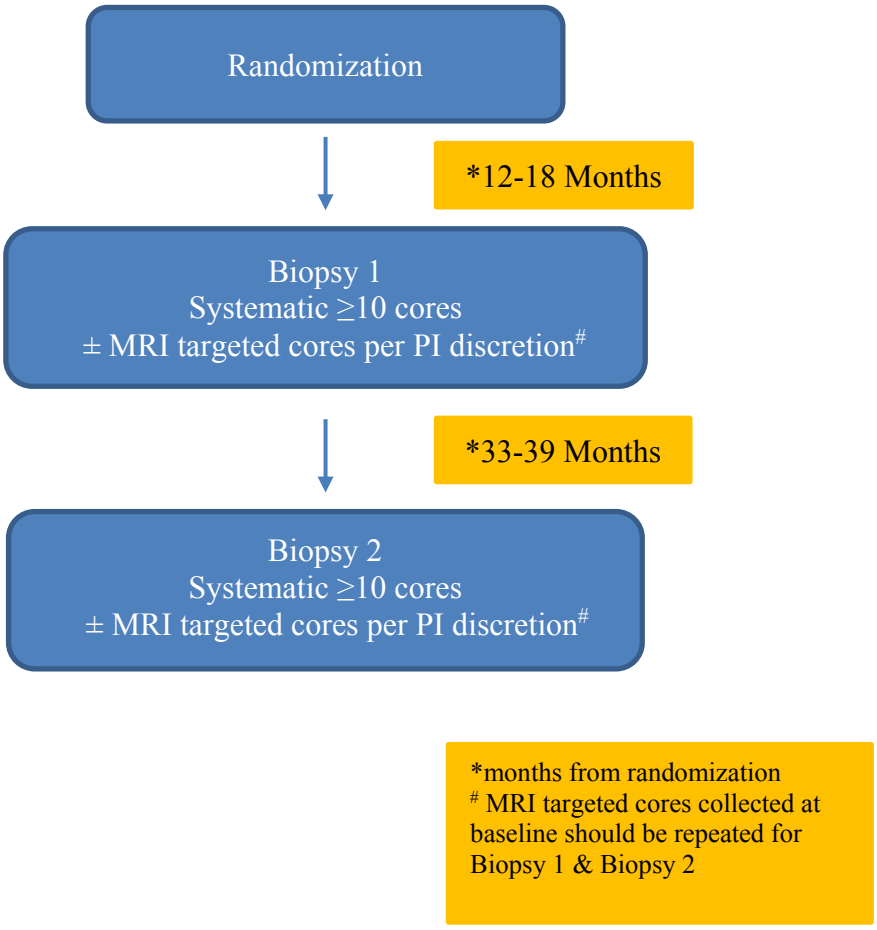
Quality of Life Due to Urinary Symptoms	Delighted	Pleased	Mostly Satisfied	Mixed	Mostly Dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	**0**	**1**	**2**	**3**	**4**	**5**	**6**

APPENDIX 6: NEW YORK CLASSIFICATION III-IV

NYHA grading		MET*
Class I	No limitations. Ordinary physical activity does not cause undue fatigue, dyspnoea or palpitations (asymptomatic LV dysfunction).	>7
Class II	Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnoea or angina pectoris (mild CHF).	5
Class III	Marked limitation of physical activity. Less than ordinary physical activity leads to symptoms (moderate CHF).	2–3
Class IV	Unable to carry on any physical activity without discomfort. Symptoms of CHF present at rest (severe CHF).	1.6

*MET (metabolic equivalent) is defined as the resting VO_2 for a 40-year-old 70kg man.[1] MET = 3.5mL O_2/min/kg body weight.

APPENDIX 7: ACTIVE PHASE BIOPSY 1 & BIOPSY 2



APPENDIX 8: DETERMINATION OF ACTIVE HEPATITIS B

Test	Result	Interpretation
Hep B Surface Antigen (HBsAg) Hepatitis B Core Antibody (HBc Total) Hep B Surface Antibody(aHBs 2 Qual	Negative Negative Negative	Negative (not to exclude)
Hep B Surface Antigen (HBsAg) Hepatitis B Core Antibody (HBc Total) Hep B Surface Antibody(aHBs 2 Qual)	Negative Positive Positive	Hep B infection resolved (not to exclude)
Hep B Surface Antigen (HBsAg) Hepatitis B Core Antibody (HBc Total) Hep B Surface Antibody(aHBs 2 Qual)	Negative Negative Positive	Vaccinated and patient is immune to Hep B virus (not to exclude)
Hep B Surface Antigen (HBsAg) Hepatitis B Core Antibody (HBc Total) Hep B Surface Antibody(aHBs 2 Qual)	Positive Positive Negative	Active HBV infection (Exclude)
Hep B Surface Antigen (HBsAg) Hepatitis B Core Antibody (HBc Total) Hep B Surface Antibody (aHBs 2 Qual)	Negative Positive Negative	Distant resolved infection, or recovering from an acute infection, false positive or occult hepatitis B (Exclude)

If aHBs2 Qual positive with or without HBc Total, patient is eligible. If HBsAg positive (regardless of all other HB panel results), patient is not eligible. All negatives are eligible as well. Isolated positive HBc Total is not eligible.

APPENDIX 9: DETERMINATION OF ACTIVE HEPATITIS C