Statistical Analysis Plan

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1.0 Approvals

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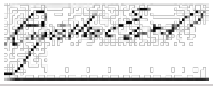
Signature / Date:	 Signed by: EwelCynthia Project Manager Reason: I am approving this document. Date & Time: 18 Oct 2019 01:06 PM -04:00 DocuSign
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2.0 Purpose

The statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Dendreon Pharmaceuticals LLC Protocol P17-1.

3.0 Scope

This SAP supplements the study protocol and provides more details on the strategy, rationale, and statistical techniques to be used towards achieving the study objectives.

The SAP outlines the following:

- Study objectives
- Study design
- Variables analyzed and analysis sets
- Applicable study definitions
- Statistical methods regarding important protocol deviations, study drug exposure, efficacy analysis, concomitant medications, adverse events handling, laboratory data and physical examinations

Any deviations from this SAP will be documented in the final Clinical Study Report (CSR).

See Appendix 1 for a list of abbreviations used throughout this document. Appendix 2 lists the mock tables, figures, and listings depicting the analyses described in this SAP.

4.0 Introduction

This SAP describes the statistical methods to be used during the reporting and analyses of data collected under Dendreon Pharmaceuticals LLC Protocol P17-1. It should be read in conjunction with the current study protocol and case report form (CRF). This version of the plan has been developed using the protocol dated 25JAN2019 and CRF dated 26JUN2019. Any further changes to the protocol or CRF may necessitate updates to the SAP.

5.0 Study Objectives

5.1 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)

5.2 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 (PROs)) between sipuleucel-T and control arms
- To evaluate the safety of sipuleucel-T in men with low to intermediate risk localized prostate cancer

5.3 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

6.0 Study Design

6.1 Overall Design

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 International Society of Urological Pathology (ISUP) Grade Group 1 or 2 adenocarcinoma of the prostate.

This study consists of 3 phases: the screening phase, the active phase, and the follow-up phase. A schematic of the study can be seen in Figure 1.

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:

- Blinded Independent Central Review (BICR) of prostate biopsy slides obtained from local pathologists (for ISUP Grade Group and Gleason Score)
- Clinical evaluations (for demographics, medical history, physical examination (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
- Patient-reported outcomes (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
- Prostate-specific antigen (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. If subjects receive the restricted therapies or procedures (Section 6.8 of the protocol), their Active Phase will stop upon receipt of any of these therapies or procedures.

Whenever possible, subjects who 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, as standard of care, a systematic prostate biopsy (≥10 cores) with or without MRI at the Investigator's discretion prior to study withdrawal. The hematoxylin and eosin

(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.

After Screening assessments are completed, eligible subjects will be randomized 2:1 to the sipuleucel-T arm or the control arm, respectively. 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 of the protocol).

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 of the protocol).

Biopsy 1 will be administered between 12 and 18 months, and Biopsy 2 will be administered between 33 and 39 months post randomization. All 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 hypothesis is met (Section 12.6.1), subjects on the control arm may be offered sipuleucel-T.

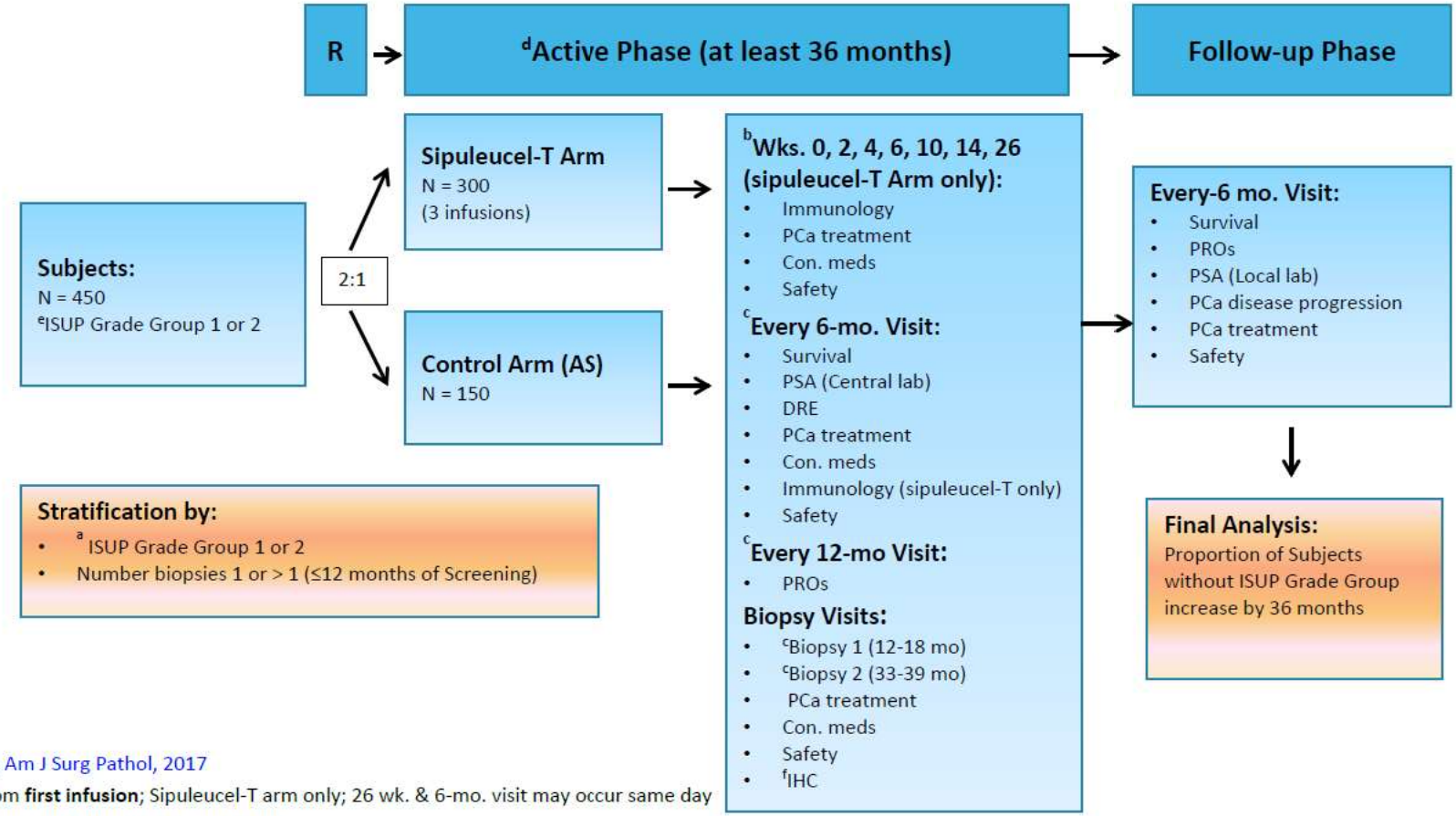
Follow-up Phase:

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 the 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

Figure 1

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)

6.2 Sample Size Considerations

The primary endpoint will be evaluated in approximately 450 subjects randomized (2:1 sipuleucel-T versus control arm). For each subject, a dichotomous variable defines Gleason group upgrade, with success defined as being 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 is that the proportion free from upgrading at 36 months in both arms is 0.70 (= 1 - 0.3) versus the specific alternative hypothesis of a greater sipuleucel-T arm upgrading-free proportion of 0.84 (= 1 - 0.16). If we denote the proportion free from upgrade at 36 months in the sipuleucel-T arm as p_S and the proportion free of upgrade at 36 months in the control arm as p_C, then the null hypothesis is that

$$H_0: p_S = p_C = 0.70$$

versus the alternative hypothesis

$$H_A: p_S \geq 0.84.$$

Written in terms of the odds ratio, the hypotheses can be depicted as

$$H_0: \frac{\frac{p_S}{(1-p_S)}}{\frac{p_C}{(1-p_C)}} = 1$$

versus the alternative hypothesis

$$H_A: \frac{\frac{p_S}{(1-p_S)}}{\frac{p_C}{(1-p_C)}} \geq \frac{\frac{0.84}{(1-0.84)}}{\frac{0.70}{(1-0.70)}} = 2.25.$$

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 at least 90% power to demonstrate the superiority of sipuleucel-T to control.

6.3 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.

Randomization will be stratified by:

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

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.

7.0 Study Endpoints, Variables and Covariates

7.1 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.

7.2 Secondary Endpoints

7.2.1 Efficacy

Per the protocol, the secondary efficacy endpoints are:

- 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), and International Prostate Symptom Score (IPSS) at baseline and 12-, 24-, and 36-month visits after randomization

The interpretations of these secondary efficacy endpoints based on the objectives, as assessed from baseline at the 12, 24, and 36 months visits post randomization, are as follows:

- Subsequent Prostate Cancer Treatment
    - Proportions of subjects with subsequent prostate cancer treatment
    - Time to the First Subsequent Prostate Cancer Treatment
- Patient Reported Outcomes (PROs). Will assess PROs at each collection point including change from baseline in the
    - MAX-PC total score and subscores for Prostate Cancer Anxiety, PSA Anxiety, and Fear of Recurrence,
    - SF-12 domain and QOL score and the SF-6D Quality adjusted Life Years index
    - EPIC-CP overall response and individual and pooled domain scores, and
    - I-PSS total scores, each of the urinary symptoms scores, and the quality of life due to urinary symptoms score.

7.2.2 Safety

Per the protocol, the secondary safety endpoint is:

- 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

The interpretation of this secondary safety endpoint is:

- Incidence of adverse events (AEs), including clinically significant laboratory abnormalities and physical examination (PE) findings reported as AEs.

7.3 Exploratory Endpoints

Per the protocol, the exploratory endpoints are:

- 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

The interpretations of these exploratory endpoints are:

- Prostate tissue biomarkers, peripheral immune biomarkers, and sipuleucel-T product parameters by histological reclassification.
- Proportion of subjects with an ISUP Grade Group change (up- or down-grade) as determined by BICR from radical prostatectomy tissue histology in the cohort of subjects having a radical prostatectomy
- Proportion of subjects with a negative biopsy at any post-randomization biopsy assessment
- 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)
- Prostate-specific antigen (PSA) velocity from randomization through study completion
- Change in prostate cancer tissue genomic profile from baseline by treatment arm

8.0 Endpoint and Variable Definitions

Unless otherwise stated, baseline refers to the last assessment prior to randomization. Study day is defined as (study date – randomization date + 1).

8.1 Efficacy Endpoints

8.1.1 Proportion of Subjects Without Gleason Group Upgrade

A subject's baseline Gleason group is reported in the ISUP grade group field on the Screening Gleason CRF page. If multiple biopsies were performed during screening, the highest ISUP grade will be used as the baseline grade.

Post-randomization biopsies are scheduled between 12 and 18 months (Biopsy 1) and between 33 and 39 months (Biopsy 2) after randomization. Primary and secondary Gleason scores from BICR of these biopsies are recorded on the Prostate Biopsy Results CRFs in the Biopsy Screen and Biopsy Screen 2 folders, respectively. Per Epstein et al (1), post-randomization ISUP grade groups can be derived from the primary and secondary Gleason scores as follows:

- ISUP Grade Group 1 – sum of primary and secondary Gleason scores ≤ 6
- ISUP Grade Group 2 – primary Gleason score = 3 and secondary Gleason score = 4
- ISUP Grade Group 3 – primary Gleason score = 4 and secondary Gleason score = 3
- ISUP Grade Group 4 – sum of primary and secondary Gleason scores = 8
- ISUP Grade Group 5 – sum of primary and secondary Gleason scores = 9-10

There may also be unscheduled or end of study biopsies post-randomization, with ISUP grade groups recorded in the "What is the Final ISUP Score" field of the ISUP End of Study Change CRF located in the Unscheduled or Early Withdrawal/End of Study folders, respectively. These will be used as post-randomization ISUP grade groups if they cannot be derived from scheduled biopsy results and if they are based on BICR. Missing scheduled Biopsy 1 ISUP grade groups will be imputed with grade groups recorded within the subjects' 12 month visit and 18 month visit dates and missing scheduled Biopsy 2 ISUP grade groups will be imputed with grade groups recorded within 90 days of the subjects' 36 month visit date. If visit dates are missing, the nominal study date will be used. For example, if the 12 month visit date is missing, it will be imputed with the date of study day 360 (12*30 days).

A subject has a Gleason group upgrade if they had an ISUP Grade Group 1 at baseline and an ISUP Grade Group 2 or higher within 36 months post-randomization or if they had an ISUP grade group 2 at baseline and an ISUP Grade Group 3 or higher within 36 months post-randomization. The primary endpoint is the proportion of subjects in the treatment arm without ISUP Gleason group upgrade within 36 months of randomization. That is, success for this endpoint is defined as not having a Gleason group upgrade at Biopsy 1 or Biopsy 2, after being assessed at least through 36 months (Biopsy 2). Subjects upgrading before 36 months, those with an upgrade at Biopsy 2, or those with missing ISUP grade group at baseline or Biopsy 2 will be counted as failures.

8.1.2 Subsequent Prostate Cancer Treatment

8.1.2.1 Proportion of Subjects with Subsequent Prostate Cancer Treatment

Types of systemic and non-systemic prostate cancer therapies are recorded in the Treatment Type field of the Systemic Prostate Cancer Therapy and Non-Systemic Prostate Cancer Therapy CRFs, respectively. Subjects may indicate more than one treatment type. Treatment types will be categorized into groups as follows:

- Surgery
  - Radical Prostatectomy
  - Orchiectomy
  - Cryotherapy or Cryosurgery
- Radiation
  - External Beam Radiation Therapy (EBRT)
  - Brachytherapy
- Androgen Deprivation Therapy (ADT)
  - GnRH agonist

- GnRH antagonist
- Enzalutamide
- Apalutamide
- Darolutamide (ODM-201)
- Bicalutamide
- Abiraterone Acetate (Zytiga)
- Abiraterone Acetate (Yonsa)

- High Intensity Focused Ultrasound (HIFU)
- Vascular Targeted Photodynamic Therapy

"Other" treatment type will be specified in the free text field "Other Specify" and will be reviewed for appropriate classification into one of the groups above. The rules of classification for "Other" treatment types will be outlined in the ADaM Reviewer's Guide.

The proportion of subjects with prostate cancer treatment in each category will be calculated for analysis.

8.1.2.2 Time to the First Subsequent Prostate Cancer Treatment

The first prostate cancer treatment is the treatment with the earliest start date on the Systemic Prostate Cancer Therapy or Non-Systemic Prostate Cancer Therapy CRF. The time to first prostate cancer therapy (weeks) is defined as (earliest start date of all prostate cancer therapies – date of randomization + 1)/7. Censoring rules applied to time to prostate cancer therapy are:

- If start date for any treatment is missing, then censor event time at randomization date
- If no post-randomization assessment for prostate cancer treatments, then censor event time at randomization date
- If no subsequent prostate cancer treatment, then censor event time at the date of the last assessment for prostate cancer treatments

8.1.3 Patient Reported Outcomes (PROs)

The following PROs are reported at baseline and at every 12-month visit. For each of the scores defined below, the change from baseline at each timepoint and maximum change (toward favorable outcome) during any assessment within 36-month after randomization, including unscheduled visit, minus the baseline score.

8.1.3.1 Memorial Anxiety Scale for Prostate Cancer (MAX-PC)

Per the MAX-PC (Appendix 3), there are 18 questions designed to better understand how subjects cope with aspects of their treatment for prostate cancer and the medical tests frequently involved in their care. Responses to the items have 4 possible integer scores ranging from 0 (Not at all) to 3 (Often), so that higher scores reflect worse symptoms. The total MAX-PC score is the sum of the scores from the 18 items and ranges from 0 to 54. The total score is missing if any of the individual scores are missing.

The 18 items are categorized into subscales of Prostate Cancer Anxiety (items 1-11), PSA Anxiety (items 12-14), and Fear of Recurrence (items 15-18). The score for each subscale is the sum of the scores from the items within each subscale so that subscale scores range from 0 to 33, from 0 to 9, and from 0 to 12, respectively. The score for each subscale is missing if any of the individual scores in the subscale is missing.

8.1.3.2 Short Form 12 Health Survey (SF-12)

The Standard SF-12 (Appendix 4) captures the subject's views about their own functional health and well-being in the past 4 weeks in 12 items. There are eight health domains measured using the SF-12 as follows:

- General Health (GH) – question 1 with a range of 1-5
- Physical Functioning (PF) – questions 2 and 3 with a range of 1-3 each
- Role-Physical (RP) – questions 4 and 5 with a range of 1-2 each
- Role-Emotional (RE) – questions 6 and 7 with a range of 1-2 each
- Bodily Pain (BP) – question 8 with a range of 1-5
- Mental Health (MH) – questions 9 and 11 with a range of 1-6 each
- Vitality (VT) – question 10 with a range of 1-6
- Social Functioning (SF) – question 12 with a range of 1-5

The SF-12 responses will be scored using OPTUM® PRO CoRE software, version 1.4 or higher, producing scores for the 8 health domains and the physical component summary (PCS) and mental component summary (MCS). Higher scores reflect higher functioning and well-being. The SF-6D index, a health state classification measure scored from 0.0 (worst health state) to 1.0 (best health state), will be derived based on the SF-12.

8.1.3.3 The Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP)

The EPIC-CP (Appendix 5) asks questions about the subject's health and symptoms in the last four weeks. There is one overall urinary function question with possible responses of No Problem, Very small problem, Small problem, Moderate problem, and Big problem. Additionally, there are 5 domains with 3 questions each and possible integer score responses ranging from 0 to 4 as follows:

- Urinary Incontinence Symptom Score – questions 2-4
- Urinary Irritation/Obstructive Symptom Score – questions 5a-5c
- Bowel Symptom Score – questions 6a-6c
- Sexual Symptom Score – questions 7-9
- Vitality/Hormonal Symptom Score – questions 10a-10c

The total score for each domain is the sum of the individual scores within the domain, i.e., the total scores in each domain range from 0 to 12 and higher scores reflect worse symptoms. The pooled scores from all domains, the sum of all domain total scores, range from 0 to 60 and capture the Overall Prostate Cancer Quality of Life Score. Scores will be set to missing if any of the individual scores are missing.

8.1.3.4 International Prostate Symptom Score (I-PSS)

The I-PSS (Appendix 6) consists of 7 questions about urinary symptoms (scores range from 0 to 5 each) and one question about quality of life (score ranges from 0 to 6), with higher scores indicating worse symptoms. The total I-PSS score is the sum of the scores from questions 1 to 7 and ranges from 0 to 35. Scores will be set to missing if any of the individual scores are missing.

8.2 Leukapheresis Variables

Number of Leukapheresis Received

Count of leukapheresis received is captured on the Leukapheresis Form at the scheduled 3 visits and unscheduled visits.

Central Venous Catheter (CVC) use

CVC use is defined as occurrence captured on the Central Venous Catheter Summary Form at any visit.

8.3 Study Drug (Sipuleucel-T) Exposure Variables

Dose Interruption

A dose interruption is defined as any interruption during the administration (infusion) of sipuleucel-T. Dose interruptions are recorded on the Sipuleucel-T - IV/Infusion Administration CRF page and indicated as a Yes response to “Was the infusion interrupted?”.

Dose Volume Infused

Actual dose volume administered is defined as the actual amount infused and is collected in the “Volume infused” field in mL.

Number of Infusions Received

Count of infusions received captured on the Infusion Summary CRF in the End of Active Phase folder.

Reasons for Less Than 3 Infusions

Reasons for receiving less than the 3 infusions planned are captured on the Infusion Summary CRF in the End of Active Phase folder.

8.4 Safety Endpoints and Variables

8.4.1 Adverse Events (AEs)

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 worsens following the start of the study.

All AEs (and SAEs) in the sipuleucel-T arm and control arm will be collected from randomization through the subject’s last study visit. For this study, treatment emergent adverse event (TEAE) is not defined. All adverse events occurring after the first leukapheresis (after randomization for the control arm) will be summarized.

8.4.2 Serious Adverse Events (SAEs)

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.

8.4.3 Clinical Laboratory Parameters

Table 1 shows the laboratory parameters that will be tested in this study. Only parameters tested by the central laboratory will be analyzed. Clinical laboratory data will be transferred from the central laboratory

and converted to International System (SI) units for analysis. Baseline laboratory parameters are those lab parameters collected closest in time, but prior to, randomization.

Table 1: Laboratory Parameters

HEMATOLOGY	CLINICAL CHEMISTRY
Hemoglobin (HgB)	Total bilirubin
Hematocrit	Alkaline phosphatase
Red blood cell count (RBC)	Lactate 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

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.

8.4.4 Physical Examination and Vital Signs

Results of physical examinations of body systems (normal/abnormal) are captured on the Physical Examinations CRF at screening. The vital signs collected on this study are height (cm), weight (kg), body temperature (°C), systolic and diastolic blood pressure (mmHg), pulse (beats/min), and respiratory rate (breaths/min). These are entered on the Vital Signs Screening CRFs in the Screening and Leukapheresis folders. Baseline physical exam results and vital signs are the last collected any time prior to randomization.

8.4.5 Electrocardiograms (ECGs)

12-Lead ECGs will be performed at screening and read locally for normality/abnormality. Any abnormalities noted at screening will be included in the Medical History CRF.

8.4.6 Digital Rectal Examinations (DREs)

Findings from DREs (abnormal – yes/no with a description of the abnormality) will be recorded at screening and every 6 months post-randomization on the Digital Rectal Examinations CRFs. Abnormal findings will be reported on the Medical History CRF. Abnormal findings post-randomization will be recorded on the Adverse Events CRF.

9.0 Analysis Sets

9.1 Intention-to-Treat (ITT)

The ITT analysis set is defined as all randomized subjects, regardless of whether any dose of treatment was received. Subjects in this analysis set will be analyzed according to the study treatment assigned at randomization. Subjects who are randomized into the sipuleucel-T arm but are replaced per protocol section 6.4 (as described below), will be included in the ITT analysis set. This analysis set will be used for the primary analyses of the primary endpoint and the secondary efficacy endpoints.

9.1.1 Replaced Subjects

Per protocol section 6.4, subjects who are randomized to the sipuleucel-T arm, but do not receive any sipuleucel-T (>0 mL) may be replaced. Thus, subjects randomized to the sipuleucel-T arm but are found to be ineligible for the study post-randomization or withdraw consent prior to receiving sipuleucel-T therapy are referred to the Medical Monitor. Should the Medical Monitor agree to replacing the subject, he marks the subject eligible for replacement in an Interactive Response Technology (IRT) system. All subjects retain the randomization number assigned. The replacement subject is assigned a new randomization number and linked to the original (replaced) subject in the IRT system.

There are three classifications for subject status in the IRT system: Randomized, Replaceable, and Replaced. A subject having a status of “Randomized” would become “Replaceable” once his replacement eligibility has been changed to “Eligible”. Further, a subject having a status of “Replaceable” would become “Replaced” once the subject has been replaced by another subject randomized into the same strata.

The Medical Monitor has the administrative access to change subject’s replacement eligibility. When a subject is marked as eligible for replacement within the same strata, the system will assign new subject for replacement with a mirror image randomization number. A randomized subject may be replaced up to 2 times.

9.2 Per Protocol (PP)

The per protocol analysis set is defined as all randomized subjects meeting inclusion and exclusion criteria requirements who have both baseline and month 36 post-randomization ISUP grade group evaluated, who have received the study treatment to which they were randomized, and who were correctly stratified into ISUP grade and number of biopsies groups. If randomized to the sipuleucel-T arm, subjects must have completed all three scheduled infusions. Subjects who are randomized into the sipuleucel-T arm without receiving any sipuleucel-T but get replaced will not be included in the PP analysis set.

Subjects who meet these criteria are considered to be evaluable for the assessment of efficacy per the protocol as planned. Subjects in this analysis set will be analyzed according to the study treatment assigned at randomization. This analysis set will be used for the sensitivity analyses of the primary endpoint and the secondary efficacy endpoints.

9.3 Safety

The safety analysis set is defined as all randomized subjects who have had any dose of study treatment, i.e., all subjects randomized to the control arm and all subjects randomized to the sipuleucel-T arm who have had some part of their first infusion. Subjects who are randomized into the sipuleucel-T arm, but are replaced per protocol section 6.4, will not be included in the safety analysis set. Subjects in this analysis set will be analyzed according to the study treatment actually received. This analysis set will be used for analysis of the safety endpoints and variables.

10.0 Interim Analyses

Not applicable. There is no interim analysis planned for this study.

11.0 Data Review

Beyond the data screening built into the PRA Data Management Plan, the PRA programming of analysis datasets, tables, figures, and listings (TFLs) provides additional data screening. Presumed data issues will be output into SAS logs identified by the word “Problem” and extracted from the logs by a SAS macro and sent to Data Management.

Review of a pre-freeze TFL run on clean subjects and a post-freeze TFL run on the frozen database allow for further data screening prior to lock. The post-freeze TFL will be discussed with the Sponsor in a data review meeting to identify any final data issues and seek corrections prior to database lock. The PRA Lead Biostatistician and the Sponsor must approve database lock.

12.0 Statistical Methods

In general, continuous variables will be summarized by number of subjects, mean, standard deviation, median, 25th percentile (Q1), 75th percentile (Q3), minimum, and maximum. The mean will be presented to one more and the standard deviation to 2 more decimal places than the precision of the variable, while the quantiles will be presented at the same precision as the original variable. Categorical variables will be summarized by frequency counts and percentages. Percentages will be presented to one decimal place.

For the primary and secondary efficacy endpoints, estimates of proportions and odds ratios will be presented with 95% two-sided confidence intervals. P-values, where required, will be based on a one-tailed test of superiority at an alpha of 0.025.

All TFLs will be presented by study treatment group. All analyses will be performed using SAS version 9.4 or higher.

12.1 Subject Population

The number and percentage of subjects in each analysis set defined in Section 9.0 will be presented overall and by study treatment arm. A by-subject listing of analysis set will be provided.

12.2 Disposition

The numbers and percentages of subjects screened, randomized and treated in the study will be presented, together with the number and percentage of subjects who terminated the study treatment prematurely and a breakdown of the corresponding reasons for termination of study drug, and the number and percentage of subjects who withdrew from the study prematurely and a breakdown of the corresponding reasons for study withdrawal. These will be presented overall and by study treatment arm. Subjects who discontinued from the study will be listed.

12.3 Important Protocol Deviations

Per PRA processes, important protocol deviations data will be entered into the Clinical Trials Management System (CTMS). The study team and the Sponsor will conduct on-going reviews of the protocol deviation data from CTMS and the resulting set of evaluable subjects throughout the study, adjusting the deviation criteria as appropriate. The subjects in the per protocol population must be finalized at the post-freeze data review meeting (or earlier), prior to database lock. Criteria for designation of a protocol deviation as important can found in the study's Protocol Deviations and Violations document, under the Guidance tab.

Important protocol deviations for subjects in the ITT population will be summarized by deviation category, overall and by study treatment arm. Important protocol deviations will also be listed.

12.4 Treatments

12.4.1 Extent of Study Drug Exposure

Exposure to leukapheresis and sipuleucel-T will be summarized in the ITT Population among the subjects randomized to sipuleucel-T. Number of reported leukapheresis, number of reported infusions, subjects reporting at least 1 leukapheresis, a CVC line, at least 1 infusion, and subjects who received 3 infusions and underwent only 3 leukapheresis will be summarized. The number and percentage of subjects with at least 1 dose interruption will be presented.

A listing of sipuleucel-T exposure will also be created. This data can be found on the Sipuleucel-T - IV/Infusion Administration CRF pages.

12.4.2 Concomitant Medications

Medications received concomitantly with study drug will be coded using World Health Organization (WHO) Drug Enhanced (version: March 2016) and categorized by Anatomical Therapeutic Chemical (ATC) Classification. Concomitant medications will be summarized by ATC code and drug name by study treatment received in the Safety population. A listing of concomitant medications will also be created.

12.5 Demographic and Baseline Characteristics

The demographic and baseline characteristics variables will be summarized in the ITT population overall and by study treatment arm.

The demographic variables include age (years), ethnicity, race, weight (kg), height (cm), smoking history, and Eastern Cooperative Oncology Group (ECOG) status.

The baseline characteristics include:

- Medical history, including abnormal ECGs and DREs (coded by MedDRA dictionary version 18.0 or higher and summarized by system organ class (SOC) and preferred term (PT));
- Abnormal physical examination findings
- Cardiovascular event risk factors
- ISUP grade group
- PSA
- Testosterone
- Viral Serology

Listings of the demographic and baseline characteristics will also be presented.

12.6 Efficacy Analyses

12.6.1 Primary Endpoint

The counts and proportions of subjects without ISUP Gleason group upgrade within 36 months of randomization will be presented by study treatment arm and overall. Exact 95% confidence intervals (CIs) for the proportions and the odds of no upgrade will also be presented. The reasons for failure (upgrade within 36 months) will be summarized as well. The exact Cochran-Mantel-Haenszel test of the null hypothesis of no difference in the odds of no ISUP grade group upgrade across treatment arms, while accounting for stratification by baseline ISUP grade group and number of biopsies, will be performed in the ITT analysis set.

12.6.1.1 Methods for Handling Dropouts and Missing Data

Missing baseline or post-baseline ISUP grade group will result in imputed failure status as defined in Section 8.1.1. These methods allow for a conservative estimate of the proportion that do not have ISUP grade group upgrade if information is not available to determine no upgrade. The pattern of missingness across study treatment arms will be explored using a Kaplan-Meier plot of missing ISUP grade group assessments across time.

12.6.1.2 Multiplicity

Not applicable. There is one test of the primary endpoint that defines the success or failure of the study.

12.6.1.3 Sensitivity Analyses

To evaluate the impact of the potential asymmetric drop-outs, the exact Cochran-Mantel-Haenszel test of the null hypothesis of no difference in the odds of no ISUP grade group upgrade across treatment arms, while accounting for stratification by baseline ISUP grade group and number of biopsies, will be repeated in the per protocol analysis set as a sensitivity analysis.

In a separate sensitivity analysis, the last observation carried forward method will be applied to the primary endpoint in the ITT analysis set. In other words, all subjects with non-missing ISUP grade group at baseline and without any upgrading within 36 months after randomization (even without any post-randomization ISUP grade group) will be counted as successes in the primary efficacy endpoint. Subjects upgrading before 36 months, those with an upgrade at Biopsy 2, or those with missing ISUP grade group at baseline will be counted as failures.

Three sipuleucel-T subjects were replaced pursuant to protocol section 6.4. Sensitivity analyses will be conducted to evaluate the impact, if any, of the inclusion of these subjects in the analysis of the primary and secondary endpoints.

12.6.1.4 Sub-group Analyses

Depending on the sample size available in subgroups, the primary endpoint will be tested in subgroups defined by

- ISUP grade group 1 and 2
- Number of biopsies within 12 months of Screening (1 and >1)
- ECOG performance status (0 and 1)
- Age by quartiles
- Race (white and non-white)
- Body mass index (BMI) (<18.5, 18.5-24.9, 25.0-29.9, and 30.0+)
- PSA density

- PSA by quartiles

12.6.2 Secondary Endpoints

12.6.2.1 Subsequent Prostate Cancer Treatment

The counts and proportions of subjects receiving subsequent prostate cancer treatment will be presented overall and by each type of cancer treatment and reason for therapy in both study treatment arms of the ITT and PP analysis sets. The exact 95% confidence intervals for the proportions will be presented as well.

Time to first subsequent prostate cancer treatment will be summarized using Kaplan-Meier (KM; Kaplan and Meier 1958) estimates for the ITT and PP analysis sets. The 25%, 50%, and 75% quartiles will be calculated and corresponding 95% CIs by the KM method. A KM plot for time to first subsequent prostate cancer treatment will be presented. The count and proportion of responding subjects who have an event or are censored will be summarized.

Subsequent prostate cancer treatment data will be provided in a listing.

12.6.2.2 PROs

For each PRO total score and pooled domain score or sub-score defined in Section 8.1.3, actual values at baseline and change from baseline at 12, 24, and 36 months visits post randomization will be summarized in the ITT and PP analysis sets in each treatment arm. The best change within 36 months post-baseline will be summarized and compared between the arms. The responses to individual question items will not be summarized except for the EPIC-CP overall urinary function question, which will be presented at baseline and its shift change presented at post-randomization.

To assess potential missing individual items in each PRO questionnaire, a sensitivity analysis in the ITT analysis set will be conducted to calculate total scores and pooled domain scores by summing up all available individual items regardless of any missing individual score.

PRO results will be provided in a listing.

12.7 Safety Analyses

12.7.1 Adverse Events

A summary of AEs, including the number and percentage of events reported, and the number and percentage of subjects

- reporting at least one AE,
- with at least one grade ≥3 AE,
- with at least one SAE,
- with at least one study drug related AE (probable or possibly related),
- with an AE leading to death

will be presented by study treatment arm in the Safety population. In the summary by worst National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 grade, the AE with the highest or most severe grade will be counted when subjects have multiple AEs in a SOC or PT.

A breakdown of the number and percentage of subjects reporting each kind of AE above, categorized by SOC and PT, will be also presented. This breakdown will be sorted by PT within SOC. Note that counting will be by subject and not by event and subjects are only counted once within each SOC or PT. This breakdown will be repeated and sorted by descending frequency of PTs in the sipuleucel-T arm for subjects reporting at least one AE and subjects reporting at least one grade ≥3 AE. This breakdown will also be

repeated by worst CTCAE grade for subjects reporting at least one AE and subjects reporting at least one grade ≥3 AE, sorted by PT within SOC.

AEs occurred within 1 day after any leukapheresis will be summarized. Similarly, AEs occurred within 1 day after any infusion will be summarized.

Listings of AEs will also be presented.

12.7.2 Deaths and Serious Adverse Events

A summary and listing of deaths from all causes will be presented for all subjects randomized, overall and by study treatment arm. See Section 12.7.1 for analyses of AEs that lead to death and SAEs.

12.7.3 Clinical Laboratory Parameters

The clinical laboratory parameters to be analyzed are listed in Section 8.3.2. Actual values at each planned visit and change in values from baseline at each post-baseline planned visit will be summarized. All laboratory results over time will be presented in a listing, including reference ranges and indications of out of range values, and an assessment of clinical significance by the Investigator. Shift tables will be used to present change in grading status from baseline.

These analyses will be performed in the Safety population, overall and by study treatment arm.

12.7.4 Vital Signs

The vital signs to be analyzed are listed in Section 8.4.4. Vital signs at each scheduled visit will be summarized along with the change from baseline to post-baseline visits. The body mass index (BMI) at each visit will also be computed using the formula BMI = weight (kg)/(height (m))^2 and summarized. A summary of abnormal vital signs will also be presented, where abnormal vital signs are systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, heart rate <60 beats/min or >100 beats/min, or temperature >37.5°C.

A listing of vital signs over time will also be presented. These analyses will be performed in the Safety population, overall and by study treatment arm.

12.7.5 Methods for Handling Dropouts and Missing Data

Below are rules for imputing missing or partial dates for analyses of medical history, AEs, and concomitant medications. Though imputed for analyses, actual dates (missing or partial) will be reflected in listings. Otherwise, there will be no imputation of missing data values. Data on subjects who withdraw early will be summarized up until the time of withdrawal.

Missing or partial dates for medical history will be imputed as follows:

- If only the day is missing, it will be imputed with the 15th day of the month.
- If both the day and month are missing, the month and day will be imputed with July 1st.
- If the date is completely missing, no imputation will be performed.

Missing or partial dates for AEs and concomitant medications will be imputed as follows:

- Start Date
    - If only the day is missing and the month and year are the same as the month and year of the first dose date, then the day will be imputed with the day of the first dose date. Otherwise the day will be imputed with the first day of the event month.
    - If both the day and month are missing and the year is the same as the year of the first dose date, then they will be imputed with the month and day of the first dose date. Otherwise they will be imputed with the July 1st of event year.

- If the start date is completely missing, the date will be imputed with the first dose date.

If the stop date is complete and the imputed start date is after the stop date, then the imputed start date will be set to the stop date.

- Stop Date
  - If only the day is missing and the month and year are the same as the month and year of the study discontinuation date, then the day will be imputed with the day of the study discontinuation date. Otherwise the day will be imputed with the last day of the event month.
  - If both the day and month are missing and the year is the same as the year of the study discontinuation then they will be imputed with the month and day of the study discontinuation date. Otherwise they will be imputed with the December 31st.
  - If the stop date is completely missing, then it will be imputed with the study discontinuation date.

Note that stop date imputation will not be applied to ongoing AEs. If the imputed stop date is greater than last the contact date, then the imputed stop date will be set to last contact date.

13.0 Validation

Quality control procedures will be documented separately in the study-specific quality control plan.

14.0 References

1. Epstein JI, Amin MB, Reuter VE, and Humphrey PA. Contemporary Gleason grading of prostatic carcinoma: An update with discussion on practical issues to implement the 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason grading of prostatic carcinoma. Am J Surg Pathol. 2017;41:e1–e7.
2. Kaplan, E.L., and Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958; 53:457-481.

Appendix 1 Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse event
ATC	Anatomic Therapeutic Classification
BICR	Blinded Independent Central Review
CRF	Case Report Form
CSR	Clinical Study Report
DMC	Data Monitoring Committee
DRE	Digital Rectal Examination
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FFPE	Formalin-Fixed Paraffin-Embedded
H&E	Hematoxylin and Eosin
HE	Health Economics
IHC	Immunohistochemistry
IRT	Interactive Response Technology
ISUP	International Society of Urological Pathology
ITT	Intention-to-treat
IVRS	Interactive Voice Response System
PE	Physical Examination
PK	Pharmacokinetic
PP	Per Protocol
PRO	Patient-reported outcome
QoL	Quality of Life
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event

Appendix 2 Tables, Figures, Listings, and Supportive SAS Output Appendices

Refer to DDCP1701-P1701X TFL Shells_v1.0.docm for the mock tables, figures, and listings described in this SAP.

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 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 5 The 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 6 International 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 7 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