Dendreon
Targeting Cancer, Transforming Lives™

**STATISTICAL ANALYSIS PLAN**

**PROTOCOL P12-2**

**Phase 2**

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

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|---|---|
| Name Of Test Drug : | Sipuleucel-T (Provenge®) |
| Protocol Number: | P12-2 |
| Sponsor: | Dendreon Pharmaceuticals, LLC |
| Statistician: | Matthew Harmon |
| Date of Approval: | 26 July 2017 |

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# 1 STUDY DESIGN

Protocol P12-2 is a randomized, open-label study designed to examine the effects on cumulative CD54 upregulation of concurrent and sequential administration of enzalutamide administered in combination with sipuleucel-T in mCRPC subjects. All subjects will be scheduled to receive three infusions of sipuleucel-T as well as a total of 52 weeks of therapy with enzalutamide either concurrently with or following administration of sipuleucel-T. This study consists of 3 phases. The screening phase will begin at the completion of the informed consent process and continue through registration. The active phase will begin at registration and continue through the post-treatment visit (30 to 37 days following the last study treatment). The long term follow-up (LTFU) phase will begin after the post-treatment visit and will continue until the subject's death or until Dendreon terminates the study.

Registered subjects will be randomized (1:1) to either the Concurrent Arm or the Sequential Arm. Subjects will be stratified by screening PSA levels (≥ 25 ng/mL, yes or no) and screening lactate dehydrogenase (LDH) levels (≥ 200 IU/L, yes or no), both obtained from the central laboratory.
Enzalutamide treatment will occur either concurrently with sipuleucel-T (concurrent arm), or following administration of sipuleucel-T (sequential arm):

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

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

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

All subjects will receive a total of 52 weeks of enzalutamide. The active phase will begin at registration and continue through the post-treatment visit (30 to 37 days following the last study

treatment). The long term follow-up (LTFU) phase will begin after the post-treatment visit and will continue until the subject's death or until Dendreon terminates the study.

All immune monitoring (IM) endpoints will be collected from all subjects who receive at least one infusion. Cellular and serological peripheral immune responses will be assessed for subjects in both arms. In both arms, IM blood samples will be collected at baseline (screening); pre-leukapheresis 2 and 3; and weeks 6, 10, 14, 20, 26, 40, and 52, with the timing of visits based on the date of the first sipuleucel-T infusion (Day 0).

During the Active phase, safety assessments in both arms will include AE monitoring, laboratory tests (complete blood count (CBC) collection serum chemistries, and liver function tests [LTFs]), vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, anticancer therapies, first opioid use for cancer-related pain, PSA monitoring, and physical examinations.

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

Sponsor's decision to terminate the study: During the first quarter of 2017, a decision was made to terminate the study during 2017 after at least 3 years of follow-up data was collected on all subjects participating in the study and still being followed. The end of follow-up period was defined as 3 years after the date that the last enrolled subject received the last infusion of sipuleucel-T.

# 2 STUDY OBJECTIVES

## 2.1 Primary Study Objective

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

## 2.2 Secondary Study Objectives

- To evaluate time to PSA Progression
- To estimate the percent of subjects who are PSA progression-free at 2 months.
- To evaluate overall survival.
- To evaluate the magnitude of peripheral immune response over time as determined by the following:
    - Peripheral PAP-specific T cell immune response to sipuleucel-T over time via T cell stimulation index from a proliferation assay.
    - T cell interferon-gamma (IFN-γ) enzyme-linked immunospot (ELISPOT) response to PA2024 and PAP
    - Humoral response by enzyme-linked immunosorbent assays (ELISA) to PA2024 and PAP

- Chemokine and cytokine production via fluorescent immunoassay (MesoScale Discovery assay system).

- To evaluate safety.

### 2.3 Exploratory Study Objectives

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

## 3 STATISTICAL CONSIDERATIONS

### 3.1 Sample Size Considerations

Approximately 100 subjects will be registered and randomized 1:1 to the Concurrent Arm or the Sequential Arm, with 50 subjects per arm.

PA2024-specific T cell proliferation responses over time will be compared between the concurrent arm and sequential arm using a repeated measurement mixed model analysis. With 43 subjects per arm, there is approximately 90% power to detect a 2-fold difference in mean response between the arms at any time point assuming a coefficient of variation of 1.25. To allow for drop-outs and subjects who may not receive 3 infusions of sipuleucel-T or at least 10 weeks of enzalutamide, approximately 50 subjects per arm will be enrolled.

In the fourth quarter of 2013 Dendreon modified the enrollment goals for this study pursuant to a corporate reorganization plan. Planned enrollment was reduced from 100 subjects to the approximately 50 subjects known to have enrolled at the time of this reorganization. Comparing PA2025-specific T cell proliferation responses over time between the concurrent arm and the sequential are with 25 subjects per arm, there is approximately 70% power to detect a 2-fold difference in mean response between the arms at any time point assuming a coefficient of variation of 1.25. A determination was made that no protocol amendment was required and on February 14, 2014, all participating sites were notified of the decision to stop enrolling subjects. Ultimately, 52 subjects were enrolled: 25 in the Concurrent Arm and 27 in the Sequential Arm

### 3.2 Analysis Populations

#### 3.2.1 Immune Response

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

### 3.2.2 Intent-to-treat (ITT)

The ITT population is defined as all randomized subjects regardless of whether they received treatment. Analysis of nonimmune response efficacy endpoints will be performed using this analysis population. Efficacy data for all randomized subjects will be included in the data listings. All the subjects in the ITT population will be analyzed according to the treatment that they are randomized to receive.

### 3.2.3 Safety

The safety population is defined as all randomized subjects who undergo at least one leukapheresis procedure or receive at least 1 dose of enzalutamide. All immune response variables and safety variables will be analyzed and summarized based on this analysis set. Immune response data and safety data for all subjects in the safety population will be included in the data listings. All the subjects in the safety population will be analyzed according to the treatment actually received.

## 3.3 Missing Data

Missing data will not be imputed for any variables except in the case of time-to-event variables. The rules for imputing missing event or censor dates are defined below (section 3.4).

## 3.4 Data Rules

- *Study Day* = [(visit date) – (date of first infusion [Day 0])]. If the infusion does not occur, Day 0 will be the date of the first leukapheresis, unless it fails, in which case, Day 0 will be the date of registration.
- *Baseline*: baseline is defined as the value closest to but prior to the randomization data.
- *Change from baseline:* change from baseline is the post-baseline value minus the baseline value.
- *Percent change from baseline:* percent change from baseline is calculated as 100 × (post-baseline value minus the baseline value) / baseline value. If the baseline or post-baseline value is missing, then the change from baseline and percent change are set to missing. If the baseline value is zero and the post-baseline is non-zero, then the percent change from baseline is set to missing. If the baseline value is zero and the post-baseline value is also 0, then the percent change from baseline is set to 0.
- *Partial Dates*: Dates missing the day, month and year and the day and month will not be imputed. However, if the month and year are present, the day may be set to the 15$^{th}$ of the month or to a date consistent with a more conservative approach to the analysis of the data point.
- *Missing event or censor date*: If the date of an event or the date of censoring is missing for a time-to-event variable, the last known study date will be used. Subjects who prematurely discontinue from the study before having the event will be censored at their last known alive date.

## 3.5 Visit Windows

Visit based data will be analyzed according to the nominal visit.

In cases where two or more assessments for the same subject have the same nominal visit label, the visit closest in time to the protocol schedule for the visit will be selected for analysis and the other visit regarded as an interim visit. If two visits are equally close in time to the scheduled visit, the visit with the 'worst-case' data will be selected. If no time collected, the worst of these assessments will be selected.

# 4 STATISTICAL METHODS

All analyses will be conducted using SAS Version 9.4 or higher.

Subjects will be stratified by screening PSA levels (≥ 25 ng/mL, yes or no) and screening lactate dehydrogenase (LDH) levels (≥ 200 IU/L, yes or no), both obtained from the central laboratory.

Due to the modification of the sample size for this study, any statistical analyses should be considered descriptive or 'exploratory.' Any statistical tests will be performed only to generate hypotheses or for data exploration.

Continuous data will be described using descriptive statistics (i.e., n, arithmetic mean, standard deviation (SD), median, minimum, and maximum). 1st quartile (Q1) and 3rd quartile (Q3) will also be presented. Categorical data will be described using the subject count and percentage in each category. For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean and median will be displayed to one level of precision greater than the data collected. Standard deviation/standard error will be displayed to two levels of precision greater than the data collected. P-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as "<0.001." If a p-value is greater than 0.999 it will be reported as ">0.999."

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values. The denominator for all percentages will be the number of subjects in that treatment within the analysis set of interest, unless otherwise specified. No adjustment for multiple comparisons across efficacy or safety variables will be performed.

For each time point where change from Baseline is evaluated for continuous variables, descriptive statistics will be displayed for the values at Baseline, values at the time point, and values for change from baseline at the time point for the set of subjects who have data at both baseline and the time point being assessed.

Any subject receiving a next anti-cancer intervention (as described in section 4.6.9) may have their efficacy observations after the date of that next anti-cancer intervention censored at the earliest date of the next intervention. Overall survival will be assessed censoring at the subjects last-known alive date.

## 4.1 Product Characterization

Product parameters to be summarized are: CD54 upregulation, $CD54^+$ cell count, and TNC count. Product parameters will be summarized descriptively (n, mean [geometric mean], standard error, median, minimum, and maximum) by Infusion (1, 2, and 3) and cumulative (summed across infusions). Cumulative product parameters will be compared between both arms using a Wilcoxon test based on the immune response population. Cumulative CD54 upregulation is the primary endpoint for the study.

## 4.2 Immune Response

To evaluate the magnitude of peripheral immune response over time as determined by the following:

- Peripheral PAP-and PA2024 specific T cell immune response to sipuleucel-T over time via T cell stimulation index from a proliferation assay.
- T cell interferon-gamma (IFN-γ) enzyme-linked immunospot (ELISPOT) response to PA2024 and PAP
- Humoral response by enzyme-linked immunosorbent assays (ELISA) to PA2024 and PAP
- Chemokine and cytokine production via fluorescent immunoassay (MesoScale Discovery assay system).

The PAP and PA2024 IFNγ ELISPOT response over time will be compared between the Concurrent Arm and the Sequential Arm, beginning with the immune sample taken at the baseline, using a repeated measurement mixed model analysis stratified by screening PSA levels and screening lactate dehydrogenase. The unit of analysis will be the background subtracted counts, computed as the median count of 3 wells exposed to antigen minus the median count of 3 wells exposed to media alone. The background subtracted counts will be ranked prior to analysis. The model will include treatment and visit as fixed effects as well as treatment by visit interaction, subject as random effect, and the two stratification factors at randomization as covariates. Visit will be considered as a categorical variable for the modeling. Several variance-covariance structures will be investigated to determine which model fit is best based on the model with the lowest Bayesian Information Criteria (BIC). Variance-covariance structures that will be investigated are unstructured (UN), auto-regressive (1) AR(1), heterogeneous autoregressive (1) (ARH (1)), compound symmetry (CS), and heterogeneous compound symmetry (CSH). Comparisons between the treatment arms at specific timepoints visits will be made using a linear contrast statement. A proper transformation (such as log-scale or rank transformation) will be applied if the data are not normally distributed. A secondary analysis of this endpoint will be based on a categorical response/no response basis. Categorical response will be defined on the basis of a threshold value determined from PA2024 ELISPOT background subtracted counts measured at baseline that ensures a sufficiently low false positive rate (i.e., 5% or less). The two treatment arms will be compared using a Fisher's exact test for a response at any time point post-baseline and by time point.

The T cell proliferation in response to PAP and PA2024, and PAP and PA2024 humoral responses of both arms will be compared using methods as described for the PA2024 ELISPOT response for IFN-γ. The unit of analysis for the T cell proliferation data is the stimulation index, defined as the median $^{3}H$ uptake of 3 wells exposed to antigen divided by the median $^{3}H$ thymidine uptake of 3 wells exposed to media. The stimulation index will be log-transformed prior to analysis. The unit of analysis for the humoral response data is the antibody titer, which will be log-transformed prior to analysis. In addition, the responder rate will be summarized by time point for the data generated from the proliferation assays, ELISPOT, and ELISA. A responder at a time point is a subject with a post-baseline result at the time point exceeding the 95$^{th}$ percentile at baseline.

AIM-V Cytokine data will be collected after each infusion of sipuleucel-T. Each cytokine parameter over time will be compared between the Concurrent Arm and the Sequential Arm, using a repeated measurement mixed model analysis. The same modeling strategy as outlined for PA2024 ELISPOT response for IFN-γ will be applied to the AIM-V cytokine data. Comparisons between treatment arms at specific time points will be made using a linear contrast statement. The data will be analyzed on a log-scale with a count of 1 added prior to taking the log so that the log will always be defined. Serum cytokine data will be analyzed in a manner similar to the AIM-V cytokine data.

### 4.3 PSA

PSA data, including change from baseline and percent change from baseline, will be summarized descriptively by treatment arm at each time point. For each time point where change from baseline is evaluated for continuous variables, descriptive statistics will be displayed for the values at baseline, values at the time point, values for change from baseline, and percent change from baseline at the time point for the set of subjects who have data at both baseline and the time point being assessed. Additionally, the maximal percent decline of serum PSA from baseline at any time point will be summarized using waterfall plots and will be compared between the treatment groups using a Wilcoxon test. Baseline will be defined as the pre-randomization PSA value. The percent of subjects with a 50% or more maximal decline in PSA at any post-baseline time point will be compared between the treatment arms using a Fisher's exact test.

Time to PSA progression will be compared between the treatment arms using a Cox regression model with terms for treatment, baseline PSA (logarithm scale), and baseline LDH (logarithm scale) in the model based on the ITT population. The estimated HR of the treatment effect and its 2-sided, 95% CI, using the sequential arm as the denominator will be provided. The percentage of subjects free of PSA progression with an associated 95% CI at landmark time points such as 6 and 12 months will be provided by treatment arm as well as pooled over treatment arms using the Kaplan-Meier method.

Time to PSA progression is defined as: 1) the time from randomization to PSA progression, and 2) the time from first enzalutamide treatment to PSA progression. Those subjects who do not experience PSA progression will be censored in the analysis at the date of their last PSA assessment. PSA progression, based on the randomization date (i.e., definition 1) will be defined for those subjects

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

## 4.4 Overall survival

Overall survival is defined as the time from randomization to death due to any cause. Subjects will be followed for survival for 3 years from the date of randomization. Those subjects alive at study end will be censored in the analysis at the day of their last documented visit or contact date. Overall survival time will be calculated as follows:

- For subjects who died prior to the study end:
  - Survival time (days) = [(death date) – (randomization date) + 1]
- For subjects who did not die prior to the study end or whose death status is unknown:
  - Survival time (days) = [(last contact date) – (randomization date) + 1]

Overall survival will be compared between the two arms using a stratified log-rank test. The estimated adjusted hazard ratio of the treatment effect and its 2-sided 95% CI, using the sequential arm as the reference group, will be generated using a Cox regression model adjusted for baseline PSA (natural log scale) and baseline LDH (natural log scale). Median survival and survival rates at specific time points will be estimated for each treatment arm using the Kaplan-Meier method, with corresponding 95% CIs.

## 4.5 Safety

Safety data will be summarized descriptively in aggregate within the safety population. All AEs observed through the post-treatment visit will be summarized. Following the post-treatment visit, only new treatment-related AEs, SAEs, seizures, and CVEs (regardless of causality) through the end of the study will be recorded and summarized. No formal statistical testing is planned for any safety summaries.

### 4.5.1 Adverse Events

Adverse events (AEs) will be summarized and listed by treatment group and by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term within each system organ class using the most current version of MedDRA at the time of study closure. Summary tables will include all AEs reported in the Concurrent Arm and Sequential Arm from the first leukapheresis.

Tables/listings to be produced will include the following:

- Incidence within system organ class (MedDRA)
- Incidence by preferred term and decreasing frequency
- Incidence by NCI CTCAE (Version 4.03) severity grade, by decreasing frequency
- Incidence of Adverse Events Occurring ≤1 Day After Infusion by preferred term and decreasing frequency
- Incidence of ≥ Grade 3 AEs, by preferred term and decreasing frequency
- Incidence of AEs that led to premature discontinuation of study therapy or study
- Incidence of SAEs within system organ class (MedDRA)
- Incidence of SAEs by preferred term and decreasing frequency
- Incidence of Cerebrovascular Adverse Events by preferred term and decreasing frequency

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

No formal statistical testing is planned for the above AE summaries. A 2-sided Fisher's exact test may be used to assess any potential trend, if appropriate, and be interpreted as hypothesis generating.

### 4.5.2 Laboratory Data

Summaries of laboratory data collected from baseline onward will include:

- Incidence of laboratory toxicities by NCI CTCAE toxicity version 4.03 grade. Separate summaries will be provided by time point, for the minimum post-baseline value, and for the maximum post-baseline value.
- Incidence of clinically significant toxicities by NCI CTCAE toxicity version 4.03. A clinically significant laboratory toxicity is defined as a toxicity with NCI grade < 3 at baseline that increased in severity to NCI grade ≥ 3. Subjects with multiple occurrences of the same toxicity are counted only once.
- Shifts from baseline. The following shifts will be computed: a) Shifts from baseline to minimum post-baseline value, b) Shifts from baseline to maximum post-baseline value, c) Shifts from baseline to last post-baseline value or end of treatment, and d) Shifts from baseline to worst post-baseline value. Laboratory values will be categorized as Normal, High, or Low based on the normal reference range.
- Summary statistics (mean, median, standard deviation, minimum, maximum) for laboratory values and their change from baseline by time point.

### 4.5.3 Vital Signs

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

Data collected pre- and post-infusion will be summarized for each of the 3 infusions. Summaries of change values will be included in these summaries where change values will be calculated as post-infusion – pre-infusion.

A summary of clinically significant abnormal vital signs at the post-infusion visit and the shift table from pre-infusion visit will be provided for each of the 3 infusions. Clinically significant abnormal vital signs are defined as:

| | | Low | High | Comments |
|---|---|---|---|---|
| Blood Pressure: | Systolic (mm Hg) | < 90 | ≥ 140 | High corresponds to NCI CTCAE Grade 2 hypertension. |
| | Diastolic (mm Hg) | < 40 | ≥ 90 | |
| Heart Rate (bpm) | | < 60 | > 100 | NCI CTCAE defines sinus brady- and tachycardia using these cut-offs (in presence of dysrhythmia) |
| Respiration (bpm) | | < 10 | > 28 | |
| Temperature (°F/°C) | | ≤ 95.0/35.0 | ≥ 100.4/38.0 | High corresponds to NCI CTCAE Grade 1 fever. Low corresponds to NCI CTCAE Grade 1 hypothermia. |

## 4.6 Other Data

### 4.6.1 Demographic and Baseline Characteristics

Demographic information and baseline disease information and characteristics will be summarized with descriptive statistics by treatment arm and overall for all analysis populations. The Wilcoxon test will be used to compare the treatment arms for continuous variables and Fisher's exact test will be used to compare the treatment arms for categorical variables.

### 4.6.2 Disposition

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

- Number of subjects randomized
- Number of subjects who had at least one leukapheresis
- Number of subjects receiving at least one infusion of sipuleucel-T
- Number of subjects receiving Enzalutamide
- Number of subjects who prematurely discontinued each study treatment
- Reason(s) for premature discontinuation of each study treatment

- Number of subjects who prematurely discontinued the study (i.e., refused further study evaluations [with the possible exception of survival status])
- Reason(s) for premature discontinuation from the study
- Number of subjects who died
- Cause of death summary
- Number of subjects in the immune response, safety analysis, and efficacy analysis sets

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

### 4.6.3 Concomitant Medications and Procedures

Concomitant medications and procedures will be presented in data listings by treatment group based on coded terms using the most current version at the time of analysis of the World Health Organization dictionary, "WHODRUG". All subjects randomized will be included. Summary tables by treatment arm will be provided with separate tables for medications and procedures started prior to the day of randomization and medications and procedures started on or after the day of randomization.

### 4.6.4 Baseline Smoking History and Cerebrovascular Event Risk Factors

Baseline smoking history regarding cigarette smoking status and cigarette smoking pack years will be summarized descriptively by treatment group. Baseline cerebrovascular event risk factors will be summarized.

### 4.6.5 Baseline Medical History

Baseline medical history will be listed.

### 4.6.6 ECOG Performance Status

ECOG performance status will be summarized descriptively by treatment group by time point. In addition, the last ECOG collected will be compared to the baseline ECOG for each subject to determine the percentage of subjects whose ECOG score improved (ECOG score lower compared to baseline), stayed the same, or worsened (ECOG score higher compared to baseline) Shifts in ECOG from baseline to post-baseline at each visit and worst post-baseline ECOG will be presented.

### 4.6.7 Protocol Deviation and Eligibility Deviation

Protocol deviations will be summarized in a table and all the protocol deviations including significant protocol deviations will be presented in a listing. Eligibility deviations will be summarized in a separate table.

### 4.6.8 Study Treatment Administration

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

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

b) Number of subjects undergoing leukapheresis for infusions 1, 2, and 3

d) Number of subjects undergoing leukapheresis more than once for infusions 1, 2, and 3

e) Number of subjects failing to receive three infusions due to insufficient TNC count and/or CD54 upregulation

f) Elapsed time between infusions

g) Elapsed time between randomization and infusion 1

Items a) through e) will be summarized by their frequency distribution and by treatment group. Items f) and g) will be summarized with descriptive statistics (mean, median, standard deviation, minimum, and maximum) by treatment group.

The duration of treatment with enzalutamide will be summarized descriptively by randomized treatment groups. The reasons for stopping enzalutamide will be summarized descriptively by randomized treatment groups.

#### 4.6.9 Anti-Cancer Interventions and Cancer-Related Opioid Use

All anticancer therapies received prior to screening and through the end of the LTFU phase were collected. Anticancer therapies included, but were not limited to, radiation, chemotherapy, hormone therapy, investigational cancer therapies, all other systemic therapies, and surgery. Each subject's first cancer-related opioid use will be collected and is defined as an opioid used for cancer-related pain that is of at least 2 consecutive days in duration.

The time to next anticancer intervention will be summarized by treatment group and is defined as the time from randomization to the first anticancer intervention as described above. Subjects who do not received any anti-cancer therapies will be censored at the last available contact date. A Cox regression model with treatment arm as the independent variable and stratified by screening PSA levels and screening lactate dehydrogenase will be used to compare the treatment arms with respect to time to first anti-cancer therapy. A similar summary will be produced for the time to first chemotherapy post randomization and time to first cancer-related opioid use.

### 4.7 Schedule of Analyses

#### 4.7.1 Interim Analysis

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

#### 4.7.2 Final Analysis

The final analysis for this trial will occur when every subject has completed approximately 3 years of survival follow-up. A nominal significance level of 0.05 will be used for all final analyses.

# 5 TABLES, LISTINGS, AND FIGURES

The content and format of all tables, listings, and figures will be specified in a separate report plan prior to final database lock of the trial.

The tables, listings, and figures specified below are intended to be a representation of the content that will be included in the clinical study report. It should be noted that the final outputs included in the actual clinical study report may not necessarily be an exact match of the content specified below.

Proposed tables. Title names and numbering subject to change.

| Number | Title |
|---|---|
| 14.1.1 | Summary of Subject Disposition |
| 14.1.2 | Summary of Eligibility Criteria Not Met |
| 14.1.3 | Summary of Eligibility Deviations |
| 14.1.4 | Summary of All Protocol Deviations |
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| 14.1.5.2 | Summary of Demographics and Baseline Characteristics – Subjects Receiving 3 Infusions of Sipuleucel-T |
| 14.1.6 | Summary of Baseline Cerebrovascular Event (CVE) Risk Factors |
| 14.2.1 | Summary of Leukaphereses and Product Infusions |
| 14.2.2 | Summary of Time Interval (Days) Between Infusions |
| 14.2.3 | Summary of the Duration of Infusions (Minutes) |
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| 14.2.7.1 | Summary of CD54 Upregulation by Infusion Number for Subjects Receiving At Least 1 Infusion of Sipuleucel-T |
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| 14.2.8.1 | Summary of $CD54^+$ Counts by Infusion Number for Subjects Receiving At Least 1 Infusion of Sipuleucel-T |
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| 14.2.10.1 | Analysis of ELISPOT Counts ($3 \times 10^5$ per PBMC) for Subjects Receiving At Least 1 Infusion of Sipuleucel-T |
| 14.2.10.2 | Estimation of ELISPOT Treatment and Visit Effects for Subjects Receiving At Least 1 Infusion of Sipuleucel-T |
| 14.2.10.3 | Analysis of ELISPOT Counts ($3 \times 10^5$ per PBMC) for Subjects Receiving 3 Infusions of Sipuleucel-T |
| 14.2.10.4 | Estimation of Treatment and Visit Effects for ELISPOT Data for Subjects Receiving 3 Infusions of Sipuleucel-T |

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# 6 REFERENCES

None