Clinical Protocol

A STUDY TO EVALUATE CHARACTERISTICS PREDICTIVE OF A POSITIVE IMAGING STUDY FOR DISTANT METASTASES IN PATIENTS WITH CASTRATION-RESISTANT PROSTATE CANCER

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Medical Monitor	**Biostatistician**	**Clinical Trial Manager**
Candice McCoy, MD	Todd DeVries, PhD	Denise Coffin, BSN, MPA
(206) 829-1630 (Telephone)	(206) 219-2714 (Telephone)	(206) 829-1550 (Telephone)
cmccoy@dendreon.com	tdevries@dendreon.com	dcoffin@dendreon.com

24 Hour Contact: (877) 336-3736

CONFIDENTIALITY STATEMENT

PROTOCOL SIGNATURE PAGE

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Amendment 2 Issue Date: 01 AUG 2014

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

Principal Investigator Name: _____

Title: _____

Address: _____

Address: _____

Address: _____

Phone: _____

Email: _____

Facsimile: _____

Signature: _____

Date: _____

PROTOCOL SYNOPSIS

Protocol Title: A Study to Evaluate Characteristics Predictive of a Positive Imaging Study for Distant Metastases in Patients with Castration-Resistant Prostate Cancer

Protocol Number: P12-1

Product IND Number: Not applicable

Clinical Phase: Not applicable

Product, Dosage Form, Route, and Treatment Regimen: No investigational product will be administered as part of this study.

Reference Product, Dosage Form, Route, and Treatment Regimen: No reference product will be administered as part of this study.

Primary Objective: To evaluate characteristics predictive of a baseline imaging study positive for distant metastases (M1) in patients with castration-resistant prostate cancer (CRPC) and no known M1.

Secondary Objectives:

- To characterize the sites of distant metastases by determining the proportion of patients with CRPC and no known M1 who receive a diagnosis of soft tissue and/or bone metastases at the time of the baseline imaging study.
- To evaluate characteristics predictive of a future imaging study positive for M1 in patients with CRPC and no distant metastases (M0) at baseline.

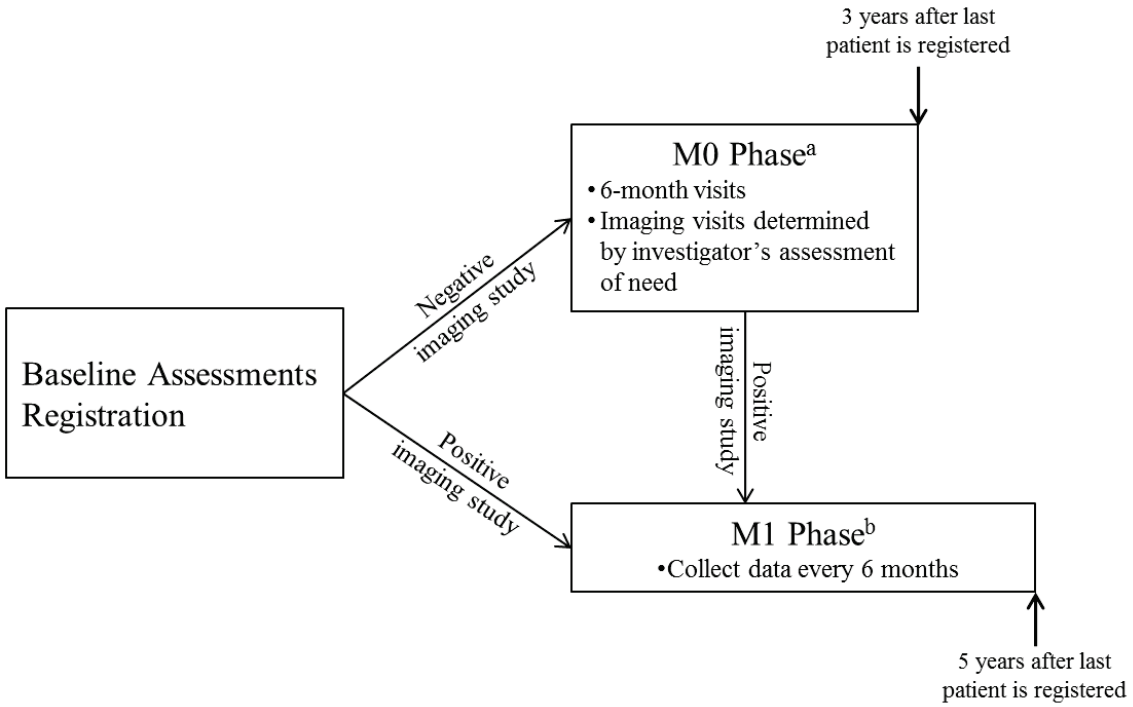
Exploratory Objectives:

- To describe the percentage of patients with CRPC and undiagnosed M1 at baseline.
- To explore biomarkers predictive of a baseline imaging study positive for M1.
- To explore biomarkers predictive of a future imaging study positive for M1 in patients with M0 CRPC at baseline.
- To evaluate characteristics predictive of a baseline imaging study positive for M1, as detected by different imaging modalities.
- To evaluate characteristics predictive of a future imaging study positive for M1 in patients with M0 CRPC at baseline, as detected by different imaging modalities.
- To describe prostate cancer treatment practice patterns for patients with M0 CRPC.
- To evaluate characteristics predictive of metastasis-free survival (MFS) in the population of patients with M0 CRPC.

- For patients diagnosed with M1 CRPC:
  - To describe the timing and sequence of prostate cancer interventions.
  - To describe changes in serum prostate-specific antigen (PSA) values, PSA progression, and PSA progression-free survival.
  - To quantify overall survival (OS) from time of diagnosis with M1 CRPC.
  - To evaluate characteristics predictive of OS.

Study Design and Duration:

This is a study to evaluate characteristics predictive of an imaging study positive for M1 in patients with CRPC. The study will include 2 phases (M0 Phase and M1 Phase) in which patients are characterized by the absence or presence, respectively, of M1. The study design is illustrated below.



[a] Every 6 months, starting from date of the patient's registration, until 3 years after the last patient is registered: ECOG performance status; current opioid analgesic use (yes/no); pain status; prostate cancer interventions; survival status; imaging studies (if needed); clinical laboratory tests, including serum PSA values; safety events; and biomarkers (AOR); all such data that have become available since the previous visit will also be collected.

[b] Every 6 months until 5 years after the last patient is registered: ECOG performance status; new sites of metastases; current opioid analgesic use (yes/no); prostate cancer interventions; survival status; clinical laboratory results, including serum PSA; and safety events; all such data that have become available since the previous time point for data collection will be collected.

Baseline

The patient population consists of patients with CRPC and no known M1. The patient will undergo the baseline visit ≤ 28 days after written informed consent is obtained. Baseline assessments will include demographics and medical history; date of diagnosis with CRPC, with confirming serum PSA values and associated hormonal therapy; prostate cancer imaging study history; Eastern Cooperative Oncology Group (ECOG) performance status; height and weight; Adult Comorbidity Evaluation-27 (ACE-27); Gleason score; serum PSA history; current opioid analgesic use (yes/no); concomitant medications; pain status (with Brief Pain Inventory [BPI]); documentation of prior and ongoing prostate cancer interventions; and imaging studies (bone and soft tissue) to determine M1 disease status. In addition, blood samples will be collected for clinical laboratory tests (alkaline phosphatase, hemoglobin, lactate dehydrogenase [LDH], serum albumin, serum PSA, and testosterone), and for additional optional research (AOR), if patient provides consent, for biomarkers potentially

predictive of treatment effects, or prognostic for MFS, OS, or an imaging study positive for metastatic disease.

Patients who have undergone an imaging study to determine the presence of M1 (bone and/or soft tissue) ≤ 3 months prior to signing the informed consent form are not eligible. However, these patients may enter the study > 3 months after their last imaging study if at that time they meet all eligibility criteria. Patients who are deemed eligible on the basis of inclusion/exclusion criteria will be registered in the trial and receive a unique identifier at that time.

Patients with baseline imaging studies confirming M0 CRPC will be entered into the M0 Phase. Patients with a baseline imaging study indicating previously unknown M1 will be entered into the M1 Phase.

M0 Phase

During the M0 Phase, there are 2 types of visits. Post-baseline imaging studies are not required in the M0 Phase and are performed if the investigator determines imaging study(ies) is/are needed to assess development of metastases (M1 CRPC). Depending on the timing of an imaging study, its results may be recorded as part of the 6-month M0 Phase study visit or part of an M0 Phase imaging visit, as described below:

- **6-month M0 Phase study visit**: A scheduled 6-month M0 Phase study visit (office visit), will occur every 6 months (± 1 month), starting from the date of the patient's registration, until 3 years after the last patient is registered. Any imaging study that occurs within 1 month of a 6-month M0 Phase study visit will be considered part of that 6-month M0 Phase study visit, and no repeat study assessments will be required.
- **M0 Phase imaging visit**: This visit occurs if, outside of the 1-month window for the 6-month M0 Phase study visit, the investigator determines imaging study(ies) is/are needed to assess development of metastases (M1 CRPC).

The choice of imaging modality will depend on the study site's standard of care; the same modality should be used for all images for a given patient until diagnosis of M1 CRPC. However, if the modality is changed to one with greater sensitivity (e.g., Tc 99m to NaF PET/CT or MRI) and diagnosis of M1 CRPC occurs at first use of a new imaging modality, an additional imaging study with the previous modality will be performed within 1 month after the positive imaging study; this additional imaging study will be reimbursed by the sponsor. However, if the modality is changed to one with lower sensitivity, an imaging study with the previous higher modality will not be performed.

Assessments for both types of M0 Phase visits include: ECOG performance status, current opioid analgesic use (yes/no), pain status (with BPI), prostate cancer interventions since the previous visit, survival status, blood samples for clinical laboratory tests (alkaline

phosphatase, hemoglobin, LDH, serum albumin, and serum PSA) and for AOR (if patient has consented to AOR), and safety events (serious adverse events [SAEs], see Safety Measures, below); all such data that have become available since the previous visit will also be collected.

M1 Phase

M1 Phase is observational. Patients will enter M1 Phase when diagnosed with M1 CRPC at registration or at any M0 Phase study visit. Patients identified with an imaging study positive for M1 disease anytime during the M0 Phase will enter M1 Phase and begin following the schedule of assessments for M1 Phase starting at the next 6-month visit. For those patients who enter M1 Phase because of a positive imaging study during M0 Phase, an ACE-27 is required to be completed within 6 months after the patient's last M0 Phase visit.

During M1 Phase, data will be collected (via clinic visits, reviews of the patient's medical record, and/or telephone calls) every 6 months (±1 month) until 5 years after the last patient is registered. At each 6-month time point during M1 phase, all data that have become available since the previous time point will be collected regarding ECOG performance status, new sites of metastases, current opioid analgesic use (yes/no), prostate cancer interventions, survival status, clinical laboratory (alkaline phosphatase, hemoglobin, LDH, serum albumin, and serum PSA) data, and safety events (SAEs, see Safety Measures, below).

In interventional clinical trials, the Prostate Cancer Working Group currently recommends measurement of serum PSA levels every 3 or 4 weeks and computed tomography (CT) or magnetic resonance imaging (MRI) every 12 weeks to assess disease progression (Scher 2008). During M1 Phase, the sponsor anticipates patients will be monitored similarly. The sponsor acknowledges that each M1 Phase patient will receive care appropriate for the treatment being administered and the standard of care in the investigator's clinical practice. At each 6-month time point for data collection during M1 Phase, all prostate cancer interventions administered during the prior 6-month period, including indication(s) for choice of therapy, starting dose, timing (start and stop dates), and rationale for starting and stopping therapy (e.g., PSA progression), will be recorded on the electronic case report form (eCRF).

The anticipated duration of the study is up to 7 years, including 2 years for accrual and up to 5 years for follow-up after the last patient is registered.

Sample Size and Population: A minimum of 2000 patients with CRPC and no known M1 and who are at least 18 years old at baseline will be registered for study participation.

Safety Measures:

The collection of adverse events (AE) will be limited to SAEs in patients who receive at least 1 partial (> 0 mL) infusion of Provenge® (sipuleucel-T) during the study and that occur at any

time from the first infusion through 30 days after the last infusion, regardless of relationship to Provenge.

Any patient who is not diagnosed with M1 CRPC and receives at least 1 partial (> 0 mL) infusion of Provenge during the study will be withdrawn from the study. Serious adverse events that occur in such patients will be recorded as described above.

For patients who withdraw consent or are determined to be lost to follow-up, the investigator will use the National Death Index (NDI) or Social Security Death Index (SSDI) to ascertain any deaths not reported in the study. The date of death, when available, will be recorded.

Statistical Considerations:

The primary analysis population will include all patients registered in the study who undergo a baseline imaging study. Patients with M0 or M1 CRPC at baseline (M0 or M1 populations, respectively) will form additional analysis populations to address different questions of interest.

The primary endpoint for the study will be the occurrence of an imaging study at baseline that is positive for M1 (yes or no) among all patients enrolled with a baseline imaging study. Logistic regression analyses will be used to analyze the primary endpoint. With 1000 patients at each of the 2 possible levels of a binary variable, for a total of 2000 patients, a variable is detectable with an odds ratio of 1.312 with 80% power using a 2-sided test at alpha = 0.05, assuming an imaging study positive for M1 at baseline in 34.95% and 29.05% of patients in level 1 and level 2 of a binary variable, respectively.

Logistic regression analyses similar to those described for the primary endpoint will be used to assess most secondary endpoints. Appropriate methods accounting for the correlation of multiple studies for a patient, such as generalized estimating equations, will be used for these analyses. Cox regression analyses incorporating information on the time to occurrence of a positive imaging study will be performed to supplement these analyses.

In this study, the collection of AEs will be limited to SAEs in those patients who have received Provenge. These events will be summarized and listed by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term within each system organ class.

No formal interim analysis is planned for this study.

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LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	adverse event
ACE-27	Adult Comorbidity Evaluation-27
ADT	androgen deprivation therapy
AOR	additional optional research
BMI	body mass index
BPI	Brief Pain Inventory
CAB	combined androgen blockade
CFR	Code of Federal Regulations
CRPC	castration-resistant prostate cancer
CT	computed tomography
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
eCRF	electronic case report form
^{18}F-NaF	sodium fluoride F 18
FDA	Food and Drug Administration
GCP	good clinical practice
ICF	informed consent form
ICH	International Conference on Harmonization
IND	investigational new drug
IRB	institutional review board
LDH	lactate dehydrogenase
LHRH	luteinizing hormone-releasing hormone
M0	no distant metastases
M1	distant metastases
MedDRA	Medical Dictionary for Regulatory Activities
MFS	metastasis-free survival
MRI	magnetic resonance imaging
NDI	National Death Index
OS	overall survival
PET	positron emission tomography
PSA	prostate-specific antigen
PSADT	PSA doubling time
RP	radical prostatectomy
SAE	serious adverse event
SSDI	Social Security Death Index
^{99m}Tc	technetium Tc 99m
US	United States

1.0 INTRODUCTION

1.1 Background

In the United States (US), prostate cancer is the most common malignancy in men. It accounted for approximately 241,740 new cases and approximately 28,170 deaths in 2012 (Siegel 2012).

At the time of diagnosis, most patients with prostate cancer have clinically localized disease with no distant metastases (M0) (Siegel 2012). However, despite radical prostatectomy (RP) or radiation therapy given with curative intent, 20% to 40% of patients eventually experience biochemical recurrence and subsequently receive androgen deprivation therapy (ADT) (Ward 2005). Although ADT leads to tumor control or regression in 80% to 85% of patients (Crawford 1989, Schellhammer 1997, Scher 1993), virtually all patients thus treated eventually develop castration-resistant prostate cancer (CRPC), which is often followed by disease progression and development of distant metastases (M1) in bones and/or lymph nodes (Scher 1996, Small 1997).

1.2 Study Rationale

Historically, technetium Tc 99m (^{99m}Tc) bone scintigraphy has been the standard method for first detection of bone metastases, and Taxotere® (docetaxel)-based chemotherapy was the only therapeutic option offering an overall survival (OS) advantage for patients with M1 CRPC. However, advances have recently been made in both detection and treatment of patients with M1 CRPC. Imaging technologies such as sodium fluoride F 18 (^{18}F-NaF), positron emission tomography (PET) / computed tomography (CT), and magnetic resonance imaging (MRI) have shown improved sensitivity and specificity compared to ^{99m}Tc scintigraphy and may lead to earlier detection of M1 disease than was previously possible (Even-Sapir 2006).

Novel treatments have recently been approved by the US Food and Drug Administration (FDA) for patients with M1 CRPC. They include Provenge® (sipuleucel-T) and Zytiga® (abiraterone acetate) for asymptomatic or minimally symptomatic disease; Xtandi® (enzalutamide) and Jevtana® (cabazitaxel) for treatment following docetaxel therapy; and Xofigo® (radium Ra 223 dichloride) for patients with symptomatic bone metastases.

Because there are many new therapies for M1 CRPC, including those indicated when no or minimal symptoms are present, and multiple imaging study modalities are available, clear guidance on the best timing, frequency, and imaging study modality for detecting M1 CRPC is essential.

Most clinicians use disease parameters such as serum prostate-specific antigen (PSA) levels and PSA doubling time (PSADT) to assess the risk of metastatic disease in individual patients and to make informed decisions regarding when to perform imaging studies (Kane 2003). Recently, however, Yu et al (2012) found that 32% of 2577 patients screened for a trial

enrolling patients with M0 CRPC did, in fact, have M1 CRPC at screening. These results indicate that M1 disease in patients with CRPC may be underdiagnosed.

Although serum PSA and PSADT have been shown to convey the relative risk of developing M1 disease (Smith 2005), other biomarkers may more accurately predict a positive imaging study (Brown 2010). Interactions between blood cells and distant metastatic cells may alter the gene expression profiles of circulating cells (Ross 2012). Recent studies have shown gene expression profiling of blood cells offers a minimally invasive approach that may be prognostic for OS and the various prostate cancer disease states, including development of M1 CRPC (Olmos 2012). Therefore, as additional optional research (AOR) in this study, blood samples will be collected at baseline and each M0 Phase visit to explore changes in gene expression profiles and their correlation with development of M1 disease.

The primary purpose of this research is to describe patient characteristics predictive of an imaging study positive for M1 in the population of patients with CRPC and no known M1. These data will contribute to clinical guidance regarding the timing and utility of imaging studies in patients with CRPC.

2.0 ETHICAL CONSIDERATIONS

The investigator will conduct the study in compliance with the Declaration of Helsinki, the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP) and the FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. The investigator will follow all relevant national, state, and local laws.

2.1 Informed Consent

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

Prior to undergoing any study assessments or procedures, all patients must provide written informed consent by signing the Informed Consent Form (ICF). The investigator or designee will provide a full explanation of the study and allow the patient to read the ICF and ask any questions that may arise. The patient will be given sufficient time to properly consider the information and to make an informed decision prior to signing the ICF. The investigator or designee will document the written informed consent process in the patient's medical record or progress notes and will provide a copy of the signed ICF to the patient.

The ICF, including any amendments, must be reviewed and approved by Dendreon staff or designees and then by the designated Institutional Review Board (IRB) prior to use in the study.

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

2.2 Institutional Review Board

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

3.0 STUDY OBJECTIVES

3.1 Primary Objective

To evaluate characteristics predictive of a baseline imaging study positive for M1 in patients with CRPC and no known M1.

3.2 Secondary Objectives

- To characterize the sites of distant metastases by determining the proportion of patients with CRPC and no known M1 who receive a diagnosis of soft tissue and/or bone metastases at the time of the baseline imaging study.
- To evaluate characteristics predictive of a future imaging study positive for M1 in patients with CRPC and no distant metastases (M0) at baseline.

3.3 Exploratory Objectives

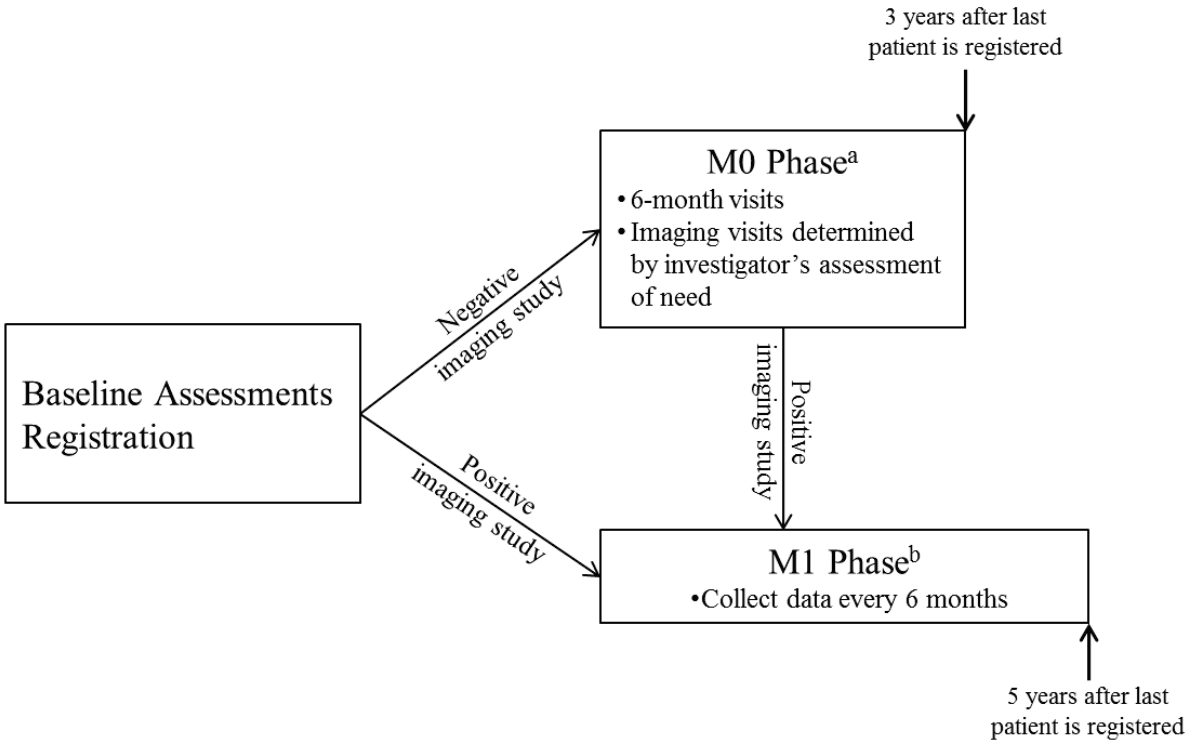
- To describe the percentage of patients with CRPC and undiagnosed M1 at baseline.
- To explore biomarkers predictive of a baseline imaging study positive for M1.
- To explore biomarkers predictive of a future imaging study positive for M1 in patients with M0 CRPC at baseline.
- To evaluate characteristics predictive of a baseline imaging study positive for M1, as detected by different imaging modalities.
- To evaluate characteristics predictive of a future imaging study positive for M1 in patients with M0 CRPC at baseline, as detected by different imaging modalities.

- To describe prostate cancer treatment practice patterns for patients with M0 CRPC.
- To evaluate characteristics predictive of metastasis-free survival (MFS) in the population of patients with M0 CRPC.
- For patients diagnosed with M1 CRPC:
  - To describe the timing and sequence of prostate cancer interventions.
  - To describe changes in serum PSA values, PSA progression, and PSA progression-free survival.
  - To quantify OS from time of diagnosis with M1 CRPC.
  - To evaluate characteristics predictive of OS.

4.0 INVESTIGATIONAL PLAN

This is a study to evaluate characteristics predictive of an imaging study positive for M1 in patients with CRPC. The study will include 2 phases (M0 Phase and M1 Phase) in which patients are characterized by the absence or presence, respectively, of M1. The study design is illustrated in Figure 1.

Figure 1: Study Design



[a] Every 6 months, starting from date of the patient's registration, until 3 years after the last patient is registered: ECOG performance status; current opioid analgesic use (yes/no); pain status; prostate cancer interventions; survival status; imaging studies (if needed); clinical laboratory tests, including serum PSA values; safety events; and biomarkers (AOR); all such data that have become available since the previous visit will also be collected.

[b] Every 6 months until 5 years after the last patient is registered: ECOG performance status; new sites of metastases; current opioid analgesic use (yes/no); prostate cancer interventions; survival status; clinical laboratory results, including serum PSA; and safety events; all such data available since previous time point for data collection will be collected.

Baseline

The patient population consists of patients with CRPC and no known M1. The patient will undergo the baseline visit ≤ 28 days after written informed consent is obtained. Baseline assessments will include demographics and medical history; date of diagnosis with CRPC, with confirming serum PSA values and associated hormonal therapy; prostate cancer imaging study history; Eastern Cooperative Oncology Group (ECOG) performance status; height and weight; Adult Comorbidity Evaluation-27 (ACE-27); Gleason score; serum PSA history; current opioid analgesic use (yes/no); concomitant medications; pain status (with Brief Pain Inventory [BPI]); documentation of prior and ongoing prostate cancer interventions; and imaging studies (bone and soft tissue) to determine M1 disease status. In addition, blood samples will be collected for clinical laboratory tests (alkaline phosphatase, hemoglobin,

lactate dehydrogenase [LDH], serum albumin, serum PSA, and testosterone), and for AOR, if patient provides consent, for biomarkers potentially predictive of treatment effects, or prognostic for MFS, OS, or an imaging study positive for metastatic disease.

Patients who have undergone an imaging study to determine the presence of M1 (bone and/or soft tissue) ≤ 3 months prior to signing the ICF are ineligible. However, these patients may enter the study > 3 months after their last imaging study if at that time they meet all eligibility criteria. Patients who are deemed eligible on the basis of inclusion/exclusion criteria will be registered in the trial and receive a unique identifier at that time.

Patients with baseline imaging studies confirming M0 CRPC will be entered into the M0 Phase. Patients with a baseline imaging study indicating previously unknown M1 CRPC will be entered into the M1 Phase.

M0 Phase

During the M0 Phase, there are 2 types of visits. Post-baseline imaging studies are not required in the M0 Phase and are performed if the investigator determines imaging study(ies) is/are needed to assess development of metastases (M1 CRPC). Depending on the timing of an imaging study, its results may be recorded as part of the 6-month M0 Phase study visit or part of an M0 Phase imaging visit, as described below:

- **6-month M0 Phase study visit**: A scheduled 6-month M0 Phase study visit (office visit), will occur every 6 months (± 1 month), starting from the date of the patient's registration, until 3 years after the last patient is registered. Any imaging study that occurs within 1 month of a 6-month M0 Phase study visit will be considered part of that 6-month M0 Phase study visit, and no repeat study assessments will be required.
- **M0 Phase imaging visit**: This visit occurs if, outside of the 1-month window for the 6-month M0 Phase study visit, the investigator determines imaging study(ies) is/are needed to assess development of metastases (M1 CRPC).

The choice of imaging modality will depend on the study site's standard of care; the same modality should be used for all images for a given patient until diagnosis of M1 CRPC. However, if the modality is changed to one with greater sensitivity (e.g., Tc 99m to NaF PET/CT or MRI) and diagnosis of M1 CRPC occurs at first use of a new imaging modality, an additional imaging study with the previous modality will be performed within 1 month after the positive imaging study; this additional imaging study will be reimbursed by the sponsor. However, if the modality is changed to one with lower sensitivity, an imaging study with the previous higher modality will not be performed.

Assessments for both types of M0 Phase visits include: ECOG performance status, current opioid analgesic use (yes/no), pain status (with BPI), prostate cancer interventions since the previous visit, survival status, blood samples for clinical laboratory tests (alkaline

phosphatase, hemoglobin, LDH, serum albumin, and serum PSA) and for AOR (if patient has consented to AOR), and safety events (serious adverse events [SAEs], see Safety Measures, below); all such data that have become available since the previous visit will also be collected.

M1 Phase

M1 Phase is observational. Patients will enter M1 Phase when diagnosed with M1 CRPC at registration or at any M0 Phase study visit. Patients identified with an imaging study positive for M1 disease anytime during the M0 Phase will enter M1 Phase and begin following the schedule of assessments for M1 Phase starting at the next 6-month visit. For those patients who enter M1 Phase because of a positive imaging study during M0 Phase, an ACE-27 is required to be completed within 6 months after the patient's last M0 Phase visit.

During M1 Phase, data will be collected (via clinic visits, reviews of the patient's medical record, and/or telephone calls) every 6 months (± 1 month) until 5 years after the last patient is registered. At each 6-month time point during M1 phase, all data that have become available since the previous time point will be collected regarding ECOG performance status, new sites of metastases, current opioid analgesic use (yes/no), prostate cancer interventions, survival status, clinical laboratory (alkaline phosphatase, hemoglobin, LDH, serum albumin, and serum PSA) data, and safety events (SAEs, see Section 7.6.18).

In interventional clinical trials, the Prostate Cancer Working Group currently recommends measurement of serum PSA levels every 3 or 4 weeks and CT or MRI every 12 weeks to assess disease progression (Scher 2008). During M1 Phase, the sponsor anticipates patients will be monitored similarly. The sponsor acknowledges that each M1 Phase patient will receive care appropriate for the treatment being administered and the standard of care in the investigator's clinical practice. At each 6-month time point for data collection during M1 Phase, all prostate cancer interventions administered during the prior 6-month period, including indication(s) for choice of therapy, starting dose, timing (start and stop dates), and rationale for starting and stopping therapy (e.g., PSA progression), will be recorded on the electronic case report form (eCRF).

The anticipated duration of the study is at least 7 years, including 2 years for accrual and up to 5 years for follow-up after the last patient is registered.

The Schedule of Assessments is presented in Table 1.

5.0 STUDY POPULATION

Men with CRPC and no known M1 disease who are at least 18 years of age at baseline are eligible. A minimum of 2000 patients will be registered in this trial. Patients must meet the following eligibility criteria to be registered in the study:

5.1 Inclusion Criteria

5.1.1. Written informed consent obtained prior to the initiation of study procedures.

5.1.2. Men ≥18 years of age.

5.1.3. Histologically documented prostatic adenocarcinoma confirmed by a pathology report from prostate biopsy or a RP specimen. Patients whose pathology reports are no longer available may be enrolled if, in the opinion of the investigator, the patient has a clinical course consistent with prostatic adenocarcinoma.

5.1.4. History of CRPC: A sequence of 2 rising serum PSA values compared to the single lowest serum PSA value (nadir), measured at least 7 days apart where the second value is ≥ 2 ng/mL (Scher 2008), in the setting of surgical or continuous medical castration (defined as testosterone ≤ 50 ng/dL with either a luteinizing hormone-releasing hormone [LHRH] agonist or antagonist as monotherapy). Patients who subsequently receive combination and/or secondary hormonal treatments (e.g., combined androgen blockade [CAB]) that reduce or control serum PSA elevation are considered to have CRPC and are eligible.

5.2 Exclusion Criteria

5.2.1. Known M1 disease: Previous imaging studies have been positive for bone or visceral metastases, or for lymph nodes having a measurable diameter ≥ 2 cm. A prostate mass or recurrence solely in the prostate bed is not considered metastatic disease (Scher 2008).

5.2.2. Undergone imaging study for metastatic prostate cancer ≤ 3 months prior to the date written informed consent is obtained. Patients with previous imaging studies may enter this trial > 3 months after their last imaging study if at that time they meet all eligibility criteria.

5.2.3. ECOG performance status ≥ 3.

5.2.4. Known malignant pleural effusions or ascites.

5.2.5. Current or prior treatment with investigational therapy for M0 CRPC, Taxotere (docetaxel), Provenge® (sipuleucel-T), Zytiga (abiraterone acetate), Xtandi (enzalutamide), Jevtana (cabazitaxel), or Xofigo (radium Ra 223 dichloride).

5.2.6. Any medical intervention or other condition which, in the opinion of the Principal Investigator or the Medical Monitor, could compromise adherence with study requirements or otherwise compromise the study objectives.

5.2.7. Treatment for or history of malignancy (stage I-IV) other than prostate cancer or non-melanoma skin cancer within ≤ 5 years.

5.3 Removal of Patients from the Study

Whenever possible, patients should remain in the study and continue with protocol-specified assessments. A patient may be withdrawn from the study if, in the investigator's clinical judgment, it is in the best interests of the patient.

Patients may discontinue their participation in the study at any time without prejudice toward their future medical care. A patient may choose to discontinue all evaluations and participation (including survival follow-up), or may discontinue all study evaluations with the exception of being followed for survival. If a patient chooses to withdraw from the study, the investigator should make every reasonable attempt to confirm the status of all ongoing SAEs meeting the criteria defined in Section 7.6.18. The date and reason for withdrawal will be recorded in the source documentation and on the eCRF.

If a patient fails to respond to requests for follow-up, the study site will (at a minimum) send a registered letter to the patient requesting contact. All attempts to resume contact (including copies of written correspondence) will be included in the source documentation. Patients who do not respond to requests for follow-up after all reasonable attempts to establish contact will be considered lost to follow-up. Data on all patients who withdraw consent or are determined to be lost to follow-up will be reviewed by the investigator through the National Death Index (NDI) or Social Security Death Index (SSDI) to ascertain any deaths not reported in the study. The date of death, when available, will be gathered from the NDI or SSDI and recorded on the eCRF.

Any patient who is not diagnosed with M1 CRPC and receives at least 1 partial (> 0 mL) infusion of Provenge during the study will be withdrawn from the study. Serious adverse events that occur in such patients will be recorded as described in Section 7.6.18.

6.0 TREATMENTS

No treatments will be administered as part of this study.

7.0 STUDY ASSESSMENTS AND PROCEDURES

Patients will provide written informed consent and those that are eligible on the basis of inclusion/exclusion criteria will be registered in the trial and receive a unique identifier at that time.

The study assessments and procedures to be performed during the study are summarized in the Schedule of Assessments (Table 1) and described in Section 7.6.

7.1 Baseline Visit

The baseline visit will occur ≤ 28 days after written informed consent is obtained and include the following:

- Demographics and medical history, including prior and current medical conditions or illness, and allergies to medications.
- Date of diagnosis with CRPC, with confirming serum PSA values and associated hormonal therapy.
- Confirmation of no current or prior treatment with investigational therapy for M0 CRPC, Taxotere (docetaxel), Provenge® (sipuleucel-T), Zytiga (abiraterone acetate), Xtandi (enzalutamide), Jevtana (cabazitaxel), or Xofigo (radium Ra 223 dichloride).
- Prostate cancer imaging study history.
- Confirmation that no imaging study to determine the presence of bone or soft tissue metastases was performed ≤ 3 months prior to the date written informed consent was obtained.
- ECOG performance status.
- Height and weight.
- ACE-27.
- Gleason score.
- Serum PSA history.
- Current opioid analgesic use (yes/no).
- Concomitant medications (prescription medications only).
- Pain status (with BPI).
- Previous and ongoing prostate cancer interventions. Prostate cancer interventions include but are not limited to radiation, chemotherapy, hormonal therapy, investigational cancer therapies, all other systemic therapies (including steroids), and surgery for prostate cancer. Record indication(s) for choice of therapy, starting dose, timing (start and stop dates), and rationale for starting and stopping therapy (e.g., PSA progression) on the eCRF.
- Bone and soft tissue imaging studies for detection of metastatic prostate cancer.
- Blood sample for clinical laboratory tests at local laboratory, as indicated in the Schedule of Assessments (Table 1).
- Blood sample for biomarker analysis, providing the patient has consented to AOR.

7.2 Registration

Registration occurs after the inclusion and exclusion criteria have been confirmed.

7.3 Scheduled 6-Month M0 Phase Study Visit

For patients in the M0 Phase, scheduled visits will occur every 6 months (± 1 month), starting 6 months from the date of the patient's registration, and will continue until 3 years after the last patient is registered. All data that have become available since the previous visit regarding the parameters listed below will be collected. Imaging studies are optional and will be determined by investigator assessment of need. Any imaging study that occurs within 1 month of a 6-month M0 Phase study visit will be considered part of that 6-month M0 Phase study visit, and no repeat assessments will be required.

The following will occur at each scheduled 6-month M0 Phase study visit:

- ECOG performance status.
- Current opioid analgesic use (yes/no).
- Pain status (with BPI).
- Prostate cancer interventions as described in Section 7.6.13.
- Survival status. The terms "alive" with the date of confirmation, "deceased", or "unconfirmed" are collected. For those patients recorded as "deceased", an additional eCRF page entitled "Date and Cause of Death" will become available. On this page, "Date of death" and "Cause of Death (check all that apply): Disease progression, Cardiac event, New primary cancer, Cerebrovascular event, and other (specify)", are listed as choices.
- Bone and soft tissue imaging studies for detection of metastatic prostate cancer (optional).
- Blood sample for clinical laboratory tests at local laboratory, as indicated in the Schedule of Assessments (Table 1).
- Serious adverse events in patients who receive at least 1 partial (> 0 mL) infusion of Provenge that occur ≤ 30 days after the last infusion, regardless of relationship to Provenge;
- Blood sample for biomarker analysis, providing the patient has consented to AOR. This sample is collected within ± 1 month of an imaging study if it occurs during the ± 1 month visit window.

7.4 M0 Phase Imaging Visits

This visit occurs if the investigator determines that imaging study(ies) is/are needed to assess development of metastatic disease (M1 CRPC) and the imaging occurs > 1 month after baseline or more than 1 month before or after a 6-month M0 Phase study visit. The following will occur during the visit:

- ECOG performance status.
- Current opioid analgesic use (yes/no).

- Pain status (with BPI).
- Prostate cancer interventions as described in Section 7.6.13
- Survival status as described in Section 7.6.14.
- Bone and soft tissue imaging studies for detection of metastatic prostate cancer.
- Blood sample for clinical laboratory tests at local laboratory, as indicated in the Schedule of Assessments (Table 1).
- Serious adverse events in patients who receive at least 1 partial (> 0 mL) infusion of Provenge that occur ≤ 30 days after the last infusion, regardless of relationship to Provenge.
- Blood sample for biomarker analysis (within ± 1 month of imaging), providing the patient has consented to AOR.

Any imaging study that occurs within 1 month of a 6-month M0 Phase study visit will be considered part of that 6-month M0 Phase study visit, and no repeat assessments will be required.

7.5 M1 Phase Data Collection

The M1 Phase will be observational. For patients in M1 Phase, data will be collected every 6 months (± 1 month) until 5 years after the last patient is registered.

At each 6-month time point during M1 Phase, all data that have become available since the previous time point regarding the parameters listed below will be collected. For patients who enter M1 Phase because of an M0 Phase study visit that includes an imaging study positive for M1, all such data that have become available since the last scheduled 6-month M0 Phase study visit will be collected.

The data to be collected during M1 Phase include:

- ECOG performance status.
- New sites of metastases.
- ACE-27 assessment (for those patients who enter M1 Phase because of an M0 Phase study visit that includes an imaging study positive for M1, an ACE-27 is required to be completed within 6 months after the patient's last M0 phase study visit).
- Current opioid analgesic use (yes/no).
- Prostate cancer interventions as described in Section 7.6.13.
- Survival status as described in Section 7.6.14.

- Clinical laboratory results (alkaline phosphatase, hemoglobin, LDH, serum albumin, and serum PSA).
- Serious adverse events in patients who receive at least 1 partial (> 0 mL) infusion of Provenge that occur ≤30 days after the last infusion, regardless of relationship to Provenge.

Data collection during M1 Phase may occur by clinic visits, reviews of the patient's medical record, or telephone calls, with the call documented in the patient's medical record. Clinic visits or telephone calls may occur by the following methods:

- Patient visit at the study site.
- Telephone call from the study site to the patient's physician.
- Telephone call between the study site and the patient.

Table 1: Schedule of Assessments—M0/M1 Phases

Event	Baseline	M0 Phase		M1 Phase
Timing	**≤ 28 days after informed consent obtained**	**From date of registration until 3 years after last patient is registered**		**From date of registration until 5 years after last patient is registered**
		6-month M0 Phase study visit (± 1 month)	**M0 Phase imaging visit as needed (> 1 month after previous study visit)**	**Data collection every 6 months (± 1 month)**
Clinical evaluations				
Demographics and medical history	X			
Date of diagnosis with CRPC, with confirming serum PSA values and associated hormonal therapy	X			
Prostate cancer imaging study history	X[ab]			
ECOG performance status	X	X	X	X
New sites of metastases		X	X	X
Height and weight	X			
Registration	X[c]			
Prognostic factors and other evaluations				
ACE-27	X			X[d]
Gleason score	X			
Serum PSA history[e]	X			
Current opioid analgesic use (yes/no)	X	X	X	X
Concomitant medications	X			
Pain status with Brief Pain Inventory	X	X	X	
Prostate cancer interventions[f]	X	X	X	X
Survival status		X	X	X
Imaging studies (bone and soft tissue)[g]	X	Optional[h]	X	
Clinical laboratory tests				
Alkaline phosphatase, hemoglobin, LDH, serum albumin	X	X	X	X[i]
Serum PSA	X	X	X	X[i]
Testosterone	X			
Safety Events[j]		X	X	X
AOR	X	X	X	

Abbreviations: ACE-27=Adult Comorbidity Evaluation-27; AOR=additional optional research (for biomarkers); CRPC=castration-resistant prostate cancer; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic case report form; LDH=lactate dehydrogenase; M0=no distant metastases; M1=distant metastases; PSA=prostate-specific antigen; SAE=serious adverse event.

[a] Patients who have undergone an imaging study to determine the presence of M1 (bone and/or soft tissue) ≤3 months prior to signing the informed consent form are not eligible.

[b] Record prostate cancer imaging studies completed from the time of biochemical recurrence after primary therapy until the baseline visit.

[c] Registration occurs after the inclusion and exclusion criteria have been confirmed

[d] For those patients who enter M1 Phase because of a positive imaging study at a 6-month M0 Phase study visit or an M0 Phase imaging visit, clinic staff will complete the ACE-27 within 6 months after the patient's most recent M0 Phase study visit and not at other time points.

[e] All serum PSA values from the date of diagnosis with CRPC until the date of written informed consent, where available, will be recorded on the eCRF.

[f] Prostate cancer interventions include but are not limited to radiation, chemotherapy, hormonal therapy, investigational cancer therapies, all other systemic therapies (including steroids), and surgery for prostate cancer. Record indication(s) for choice of therapy, starting dose, timing (start and stop dates), and rationale for starting and stopping therapy on the eCRF.

[g] The number and sites of bone, regional or distant nodal or visceral metastases, if present, will be recorded on the eCRF. Choice of imaging modality depends on study site's standard of care; the same modality should be used for all images for a given patient until diagnosis of M1 CRPC. However, if modality is changed and diagnosis of M1 CRPC occurs during first use of a new imaging modality, an additional imaging study with the previous modality will be performed within 1 month of the positive imaging study; this additional imaging study will be reimbursed by the sponsor. However, if the change is from a higher to a lower sensitivity modality, the higher sensitivity modality will not be repeated.

[h] Frequency of imaging studies will be at investigator's assessment of need. Imaging studies performed within 1 month of a 6-month M0 Phase study visit will be considered part of that visit.

[i] For patients in M1 Phase, clinical laboratory results, including serum PSA data, that have become available since the previous time point for data collection will be recorded on the eCRF.

[j] For patients who receive at least 1 partial (>0 mL) infusion of Provenge, record SAEs that occur ≤ 30 days after the last infusion, regardless of relationship to Provenge.

7.6 Procedures and Assessments

7.6.1 Demographics and Medical History

The following demographic data will be recorded on the eCRF for all patients: date of birth, ethnicity, and race.

The following medical history information will be recorded on the eCRF at the baseline visit: historic and current medical conditions or illness, allergies to medications, and prior prostate cancer interventions, including therapies and surgical procedures.

7.6.2 Date of Diagnosis with CRPC

The date of diagnosis with CRPC will be confirmed at the baseline visit. A sequence of 2 rising serum PSA values (compared to a nadir value) measured at least 7 days apart where the second value is ≥ 2 ng/mL (Scher 2008), in the setting of surgical or continuous medical castration (defined as testosterone ≤ 50 ng/dL with either an LHRH agonist or antagonist as monotherapy) is required. Patients who subsequently receive combination and/or secondary hormonal treatments (e.g., CAB) that reduce or control their serum PSA elevation are considered to have CRPC and are eligible for the study.

The date of diagnosis with CRPC is defined as the date of the first serum PSA value above nadir in the sequence of serum PSA values used to confirm the presence of CRPC. The date of diagnosis with CRPC will be recorded on the eCRF.

7.6.3 Prostate Cancer Imaging Study History

At the baseline visit, all previous imaging studies for prostate cancer (type and date) that were completed from the time of biochemical recurrence after primary curative therapy until the baseline visit will be recorded on the eCRF. For patients who have not received primary curative therapy, all imaging studies completed from the time of diagnosis until the baseline visit will be recorded on the eCRF.

Biochemical recurrence is defined as a rising serum PSA after primary curative therapy as follows:

- If primary therapy was RP (with or without external beam radiation therapy), rising serum PSA is defined as 2 consecutive rising values above 0.2 ng/mL, each taken ≥ 3 weeks apart, and the last value is ≥ 0.5 ng/mL.
- If primary therapy was external beam radiation, rising serum PSA is defined per the Phoenix definition (Roach 2006), i.e., as 2 consecutive rising values, each taken ≥ 3 weeks apart and above the serum PSA nadir plus 2.0 ng/mL.

7.6.4 Eastern Cooperative Oncology Group Performance Status

ECOG performance status (Appendix 1) will be collected and recorded on the eCRF at the baseline visit, scheduled 6-month M0 Phase study visits, M0 Phase imaging visits, and time points for data collection in M1 Phase.

7.6.5 New Sites of Metastases

At all M1 data collection time points, new sites of visceral, nodal or bone metastases will be recorded on the eCRF.

7.6.6 Height and Weight

Height and weight will be measured at the baseline visit and recorded on the eCRF.

7.6.7 Adult Comorbidity Evaluation

The ACE-27 (Appendix 2) is used to identify the important medical comorbidities and determine the overall comorbidity score. For all patients, clinic staff will complete the ACE-27 at the baseline visit. For those patients who enter M1 Phase because of a positive imaging study during M0 Phase, an ACE-27 is required to be completed within 6 months after the patient's last M0 Phase visit.

7.6.8 Gleason Score

At the baseline visit, Gleason scores from initial prostate cancer diagnosis and, if available, following grade change after RP, will be collected and recorded on the eCRF. The highest and second highest values will be recorded.

7.6.9 Prostate-specific Antigen History

At the baseline visit, all serum PSA values, as available, from the date of diagnosis with CRPC as defined in the protocol until the date written informed consent is obtained will be recorded on the eCRF. Serum PSA values documented in a medical record are acceptable.

7.6.10 Current Opioid Analgesic Use

At the baseline visit and all M0 and M1 data collection, current opioid use (yes/no) will be recorded on the eCRF.

7.6.11 Concomitant Medications

At the baseline visit, the patient's current prescription medications and indications will be recorded on the eCRF. Only prescription medications will be recorded.

7.6.12 Pain Status

At the baseline visit, scheduled 6-month M0 Phase study visits and M0 Phase imaging visits, pain status will be measured with the BPI (Appendix 3) and the information will be recorded on the eCRF.

7.6.13 Prostate Cancer Interventions

At the baseline visit, all previous and ongoing prostate cancer interventions will be recorded. From registration until the patient is discontinued from or completes the study, all prostate cancer interventions will be recorded on the eCRF. Prostate cancer interventions include but are not limited to radiation, chemotherapy, hormonal therapy, investigational cancer therapies, all other systemic therapies (including steroids), and surgery for prostate cancer. Information collected regarding prostate cancer interventions will include the indication(s) for choice of therapy, starting dose, timing (start and stop dates), and rationale for starting and stopping therapy (e.g., PSA progression).

7.6.14 Survival Status

Survival status is assessed in patients at all M0 and M1 data collection time points. The terms "alive" with the date of confirmation, "deceased", or "unconfirmed" are collected. For those patients recorded as "deceased", an additional eCRF page entitled "Date and Cause of Death" will become available. On this page, "Date of death" and "Cause of Death (check all that apply): Disease progression, Cardiac event, New primary cancer, Cerebrovascular event, and other (specify)", are listed as choices.

7.6.15 Imaging Studies

Patients will undergo bone imaging studies (e.g., MRI, ^{99m}Tc bone scintigraphy or ^{18}F-NaF PET/CT) and soft tissue imaging studies (e.g., contrast-enhanced abdominal and pelvic CT or MRI) at the baseline visit and M0 Phase visits in order to detect any M1 disease. The imaging modality will be determined based on the study site's standard of care and will be recorded on the eCRF.

The presence of M1 disease will be determined by the presence of bone, regional or distant nodal, or visceral metastasis, as follows:

- Bone metastasis

  Patients with one or more unequivocal bone lesions as identified by site's standard for imaging modality will be considered to have M1 CRPC. Patients with equivocal scans determined by standard imaging (e.g., ^{99m}Tc bone scan) will be evaluated by more sensitive imaging modalities such as CT, ^{18}F-NaF PET/CT, or MRI within 1 month of the equivocal scan to confirm M1 disease status (Adams 2011).

- Regional or distant nodal metastasis

  Patients diagnosed with lymph node(s) (measuring ≥ 2 cm on the greatest diameter) in either regional pelvic or distant lymph nodes will be considered to have M1 disease (Scher 2008).

  Examples of regional lymph nodes include: hypogastric, obturator, internal and external iliac and lateral, presacral and promontory sacral lymph nodes (Adams 2011).

  Examples of distant lymph nodes, which lie above the bifurcation of the common iliac arteries and outside of the confines of the true pelvis, include: aortic, common iliac, deep inguinal, superficial inguinal, supraclavicular, cervical, scalene, and retroperitoneal lymph nodes (Adams 2011).

- Visceral metastasis

  Patients diagnosed with metastasis to liver, lung, brain, or other solid organ will be considered to have M1 disease.

The number and sites of bone, regional or distant nodal, or visceral metastases, if present, will be recorded on the eCRF.

The same bone and soft tissue imaging modalities utilized at baseline should be used for all images for a given patient until diagnosis of M1 CRPC. However, the imaging modality may be changed at the investigator's discretion, assuming that subsequent imaging studies are performed with the new modality. If the diagnosis of M1 CRPC occurs during the first use of a new imaging modality (e.g., first use of ^{18}F-NaF PET/CT imaging after previous use of ^{99m}Tc bone scintigraphy), an additional imaging study with the previous imaging modality will be performed within 1 month after the positive imaging study to allow comparison of the sensitivity and specificity of the 2 methods; this additional imaging study will be reimbursed by the sponsor. However, if the change is from a higher to a lower sensitivity modality, the higher sensitivity modality will not be repeated.

7.6.16 Clinical Laboratory Tests

Blood samples for assessment of the following parameters will be obtained at the baseline visit and all M0 Phase visits unless otherwise noted:

- Alkaline phosphatase
- Hemoglobin
- Lactate dehydrogenase (LDH)
- Serum albumin
- Serum PSA
- Testosterone (baseline visit only)

Local laboratories will be used for the above laboratory tests and the results will be recorded on the eCRF.

At each time point for data collection during M0 phase and M1 phase, clinical laboratory (alkaline phosphatase, hemoglobin, LDH, serum albumin) and serum PSA data that have become available since the previous time point will be recorded in the eCRF. Blood samples for clinical laboratory or serum PSA values will not be collected during M1 Phase.

7.6.17 Additional Optional Research for Biomarkers

Patients will be given the opportunity to consent to allow Dendreon to collect investigational blood samples for use in AOR, which will include biomarker analysis and other additional testing. The samples will be analyzed for biomarkers that may be predictive of treatment effects and/or prognostic for MFS, OS, or an imaging study positive for metastatic disease. The samples will be retained for an indefinite period of time. They may be used for gene and gene expression analysis, and retained samples may be sent to outside laboratories for testing. Retained samples will be used for research only, and will not be sold. AOR blood samples will not be identified using patient names or other personal identifiers. Neither the patient nor the study site will receive AOR testing results.

For patients who provide consent for AOR, a whole blood sample will be obtained at the baseline visit and each M0 Phase visit (at scheduled 6-month M0 Phase study visits and M0 Phase imaging visits [within ± 1 month]) until diagnosis with M1 CRPC, or the M0 Phase patient completes or is discontinued from the study. Such samples will not be collected from patients who do not provide additional consent for AOR.

7.6.18 Serious Adverse Events

The collection of adverse events (AEs) will be limited to SAEs in patients who receive at least 1 partial (> 0 mL) infusion of Provenge during the study and that occur at any time from the first infusion through 30 days after the last infusion, regardless of relationship to Provenge.

Any patient who is not diagnosed with M1 CRPC and receives at least 1 partial (> 0 mL) infusion of Provenge during the study will be withdrawn from the study. Serious adverse events that occur in such patients will be recorded as described above.

<u>Definition of a Serious Adverse Event</u>

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, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered

SAEs when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Categories for Ranking the Relationship of a Serious Adverse Event

None:	The SAE is clearly related to other factors, such as the patient's clinical state, environmental factors, or other modes of therapy or concomitant drugs administered to the patient.
Possible:	The SAE follows a reasonable temporal sequence from a study-required procedure or administration of Provenge, but could readily have been produced by the patient's clinical state, environmental factors, or other modes of therapy or concomitant drugs administered to the patient.
Probable:	The SAE follows a reasonable temporal sequence from a study-required procedure or administration of Provenge and cannot readily have been produced by the patient's clinical state, environmental factors, or other modes of therapy or concomitant drugs administered to the patient.

Reporting Requirements for a Serious Adverse Event

Serious adverse events that meet the criteria for collection during the study, as outlined in this section, will be reported to Dendreon or designee. Serious adverse events must be reported to Dendreon or designee within 24 hours of first knowledge of the event by completing the SAE form. The SAE information must be reported to Dendreon or designee within 24 hours by telephone or facsimile, and a completed written report using Dendreon's SAE Report Form must be submitted by facsimile within 3 business days to:

Dendreon Corporation
Attn: Safety Manager
Facsimile: (877) 630-5352
Telephone: (800) 349-8086
Email: DendreonSafety@unitedbiosource.com
Telephone (24-hour access): (877) 336-3736

Significant new information regarding an ongoing SAE and the resolution must be sent to Dendreon or designee within 3 business days of awareness of the new information on the SAE Report Form.

Expedited Reporting Requirements

Dendreon will notify the FDA or other applicable regulatory agencies and health authorities of any SAE in this study associated with the use of Provenge that is unexpected and at least possibly related. Such notification will be provided within 15 calendar days after Dendreon's initial receipt of the information for all SAEs.

8.0 STATISTICAL METHODS

8.1 Sample Size Considerations

This study will identify patient characteristics at the time of the baseline imaging study that are predictive of an imaging study positive for M1 in patients with CRPC and no known M1. A minimum of 2000 patients will be registered in this study. This sample size is based on the following considerations.

The primary endpoint for the study will be the occurrence of a positive imaging study for M1 at baseline (yes or no), a binary variable. All patients with a baseline imaging study will be included in the analysis of the primary endpoint. Yu et al (2012) found that 32% of 2577 men screened for a trial enrolling patients with CRPC thought to be M0 did, in fact, have M1 CRPC, and it is anticipated that this study will have a similar finding. With 1000 patients at each of the 2 possible levels of a binary variable, for a total of 2000 patients, the variable is detectable with an odds ratio of 1.312 with 80% power using a 2-sided test at alpha = 0.05, assuming an imaging study positive for M1 at baseline in 34.95% and 29.05% of patients in level 1 and level 2 of the binary variable, respectively. However, a binary variable that is distributed at a ratio of 1:5 at baseline would allow for an odds ratio of 1.422 to be detected with 80% power assuming an imaging study positive for M1 at baseline in 38.5% and 30.6% of the patients in level 1 and level 2 of the binary variable, respectively.

8.2 General Considerations

8.2.1 Analysis Populations

The all-enrolled population will include all patients registered in the study. The primary analysis will be based on the primary analysis population, which will include patients in the all-enrolled population who undergo a baseline imaging study. In addition, patients with M0 or M1 CRPC at baseline (M0 or M1 populations, respectively) will form separate analysis populations to address different questions of interest.

8.2.2 Interim Analysis

No formal interim analysis is planned for this study. Periodic summarization of the data will be performed on an ongoing basis. However, as there are no formal hypotheses being tested in this protocol, no significance-level adjustments will be made for statistical testing or estimation procedures that may be utilized.

8.2.3 Control Groups

There is no reference product in this protocol. Descriptive comparisons may be made to external datasets.

8.3 Analysis of Endpoints

8.3.1 Primary Endpoint

The primary endpoint for the study will be the occurrence of an imaging study at baseline that is positive for M1 (yes or no) among all patients enrolled with a baseline imaging study. Logistic regression analyses will be used to analyze the primary endpoint. Univariate logistic regression analyses will be performed separately for each variable of interest. A multivariate logistic regression analysis will be performed including all variables of interest. A stepwise regression model selection procedure will be used to identify a model that includes explanatory factors that are independently predictive of the occurrence of a positive imaging study. The logistic regression model will be used to develop a formula for predicting the probability of a positive imaging study given specific values for the variables included in the final model.

Variables that will be considered for inclusion in the model are age, race, ethnicity, duration of disease in years from initial diagnosis to study registration, total Gleason score at diagnosis, post-RP Gleason score total, baseline ECOG performance status, baseline hemoglobin, baseline alkaline phosphatase, baseline LDH, baseline serum albumin, baseline testosterone, baseline serum PSA, baseline PSADT, first serum PSA demonstrating CRPC, baseline body mass index (BMI), prior systemic therapy (yes or no), prior ADT (yes or no), prior RP (yes or no), and prior orchiectomy (yes or no), current opioid analgesic use (yes/no), and number of prior scans. Baseline BPI scores, including worst pain in last 24 hours, least pain in last 24 hours, average pain in last 24 hours, and pain right now, will also be considered for inclusion.

The above list of variables will be considered for inclusion in the final model; however, each variable will be initially screened and will be dropped from consideration for inclusion in the final model if it is shown to have little predictive value as a univariate predictor. Candidate variables for the final model will be determined by the following algorithm. A univariate logistic regression will be applied for each individual variable and all variables with $p < 0.25$ will be considered as candidate variables for the final model. Interaction terms will also be considered for the final model. Interaction terms will be considered as candidates for the final model if the p-value for the interaction term is less than 0.25 from a model with predictor variables of variable a, variable b, and interaction of variable a and b. Only variables with $p < 0.25$ from the univariate model screening procedure as discussed above will be considered for determining the list of interaction terms for consideration in the final model.

All candidate variables, including interaction terms identified by the algorithm discussed above, will be entered into the stepwise model selection procedure. The criteria for a variable to enter the model will be $p < 0.05$ and variables will be retained in the model during the elimination step if $p < 0.10$. The final model will include all terms identified from the stepwise selection procedure and will also include all main effect terms for any interaction variables identified in the stepwise model selection procedure.

Although the above list of variables for consideration for inclusion in the model is a comprehensive one, addition or deletion of variables for consideration may occur. Therefore, the complete list of candidate variables for inclusion in the model will be provided in the final statistical analysis plan.

8.3.2 Secondary Endpoints

The proportion of patients who receive a diagnosis of M1 CRPC at the time of the baseline imaging study will be categorized as metastatic due to soft tissue (nodal and/or visceral) metastases, bone metastases, or both. The percentage of patients in each category will be computed based on the primary analysis population.

Logistic regression analyses, similar to the analyses described for the primary endpoint, will be used to identify characteristics predictive of an imaging study positive for M1 in the M0 population. Analyses will be performed using baseline information only as predictor variables with the outcome variable as a positive imaging study (yes/no) at any post-baseline time point. In addition, an analysis will be performed on the M0 population using all imaging studies collected in the study as the outcome variable (positive=yes/negative=no) with predictor variables associated with each imaging study. Appropriate methods accounting for the correlation of multiple studies for a patient, such as generalized estimating equations, will be used for this analysis. Cox regression analyses incorporating information on the time to occurrence of a positive imaging study will be performed to supplement these analyses.

8.3.3 Exploratory Endpoints

Prostate cancer treatment practice patterns will be summarized descriptively for patients with M0 CRPC and M1 CRPC. Prostate cancer interventions prior to study entry will be summarized. Additionally, the timing and sequence of prostate cancer interventions during the study will be summarized.

The identification of biomarkers in the M0 population that are predictive of an imaging study positive for M1 will be performed using logistic regression and Cox regression, as previously described. These analyses will be performed for both the primary endpoint (a positive imaging study at baseline) and the endpoint of a positive imaging study at any post-baseline time point.

The percentage of patients with CRPC with previously undiagnosed M1 at baseline will be calculated as 100 times the number of patients in the M1 analysis population divided by the total number of patients in the study.

Logistic regression analyses will be used to determine patient characteristics in the M0 population that are predictive of a positive imaging study at baseline as detected with different imaging modalities. The differing imaging modalities include MRI, ^{99m}Tc bone scintigraphy, or ^{18}F-NaF PET/CT for bone imaging; and contrast-enhanced abdominal and pelvic CT or MRI for soft tissue imaging. For each imaging modality, multivariate logistic regression modeling will be used to identify factors that are independently predictive of a positive imaging study. These analyses will be performed for both the primary endpoint (a positive imaging study at baseline) and for the endpoint of a positive imaging study at any post-baseline time point.

Metastasis-free survival will be defined as time from the date of the baseline imaging study to the first occurrence of M1 or death due to any cause in the M0 population. Patients who are not observed to develop M1 or who do not die will be censored at the last time observed for determination of M1. Only patients who are confirmed with M0 CRPC at study entry will be included in the analysis. Cox regression analyses will be used to analyze the MFS endpoint. Univariate Cox regression analyses will be performed separately for each baseline variable of interest. A multivariate Cox regression analysis will be performed including all baseline variables of interest. Various model selection procedures will be investigated, including forward, backward, and stepwise regression to identify a model that includes explanatory factors that are independently predictive of development of M1 or death. Supplementary analyses, including time-varying covariates of ECOG performance status and laboratory parameters, will also be provided.

Overall survival will be defined as the time from diagnosis with M1 CRPC until death. Patients who do not die will be censored at the last date they were known to be alive. Analyses similar to those described for MFS will be performed in the M1 population to determine patient characteristics that can be used to predict OS. The Kaplan-Meier method will be used to quantify the survival duration from the time of diagnosis with M1 CRPC. In addition, the effect of prostate cancer interventions and their sequencing on OS will be evaluated using a Cox regression analysis with time-varying covariates.

The timing and sequence of prostate cancer interventions will be summarized descriptively for the M1 population. The time to prostate cancer interventions will be defined as the time from the date of diagnosis with M1 CRPC until initiation of the prostate cancer intervention.

Changes in serum PSA levels during treatment for M1 CRPC will be summarized descriptively for the M1 population. For treatments with sufficient patient numbers, changes in serum PSA levels over time, PSA progression, and PSA progression-free survival will be

summarized descriptively by treatment. The maximum percentage reduction in serum PSA levels will also be summarized descriptively by treatment.

8.4 Safety Events

In this study, the collection of AEs will be limited to SAEs and meeting the criteria defined in Section 7.6.18. Serious adverse events will be summarized and listed by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term within each system organ class. Serious adverse events that occur multiple times for a patient will be counted only once per patient in incidence summary tables. A listing of SAEs at least possibly related to Provenge will be provided.

8.5 Demographic and Baseline Characteristics

Demographic information and baseline disease characteristics will be summarized. Separate summaries will be provided for the primary analysis, M0, and M1 populations.

8.6 Patient Disposition

The disposition of all patients screened and enrolled in the study will be summarized in aggregate. Reasons for screening failure and premature study discontinuation will be summarized.

8.7 Concomitant Medications

Concomitant medications will be presented in data listings.

9.0 REGULATORY REQUIREMENTS

9.1 Pre-Study Documentation

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

- Copy of signed Protocol Signature Page.
- Copy of curriculum vitae of Principal Investigator, updated within the past 2 years.
- Copy of current medical license for the Principal Investigator.
- Copies of financial disclosure forms for all investigators.
- Copy of the IRB approval letter for the study.
- Documentation of the IRB approval of the ICF and copy of the IRB-approved ICF.
- Copy of IRB-approved patient materials.
- IRB membership list or Department of Human and Health Services Assurance Number.

9.2 Investigator Obligations

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

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

All investigators must complete and return Financial Disclosure statements (including information on spouses, legal partners, or dependent children) before study initiation. Investigators must promptly update this information if any relevant changes occur in the course of the study or in the year after the study is completed (21CFR§54.4). In addition, the Principal Investigator is responsible for providing Dendreon an adequate final report shortly after study participation is complete, in accordance with 21CFR§312.64.

9.3 Patient Confidentiality

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

Individual patient identities will not be disclosed in any report or publication related to the study, and will not be recorded on any eCRFs maintained by Dendreon.

10.0 PROTOCOL MANAGEMENT AND ADMINISTRATIVE CONSIDERATIONS

10.1 Study Documentation

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

- Patient files, containing the completed eCRFs, supporting source documentation from the medical record including laboratory data, pathology reports, and the signed ICF.

- Regulatory files, containing the protocol with all amendments and protocol signature pages, copies of all other regulatory essential documentation, and all correspondence between the study site and the IRB and sponsor.

Records are to be available for at least 2 years after study completion and the FDA is so notified.

10.2 Data Collection

Data will be entered into the electronic data capture (EDC) system. Trained study personnel will be responsible for entering data on the observations, tests, and assessments specified in the protocol into the EDC system and according to the eCRF Instructions. The eCRF Instructions will also provide the study center with data entry instructions. Data entered in the EDC system will be immediately saved to a central database and changes tracked to provide an audit trail.

10.3 Protocol Interpretation and Compliance

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

10.4 Study Monitoring

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

10.5 Quality Assurance

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

In addition, inspections by health authority representatives and/or the IRB may occur at any time. The investigator must inform Dendreon Clinical Affairs or designee of any such inspection immediately. Direct access to source documents and medical records will be required for audit and inspections.

10.6 Disclosure of Data and Publication

The investigator or others working on the study will submit all proposed publications, papers, abstracts or other written materials related to the study, or an outline of any proposed oral presentation with respect thereto, to Dendreon at least 1 month prior to (i) submission of such written materials for publication, or (ii) any proposed oral disclosure to a third party. Dendreon shall have the right to comment on such written material or outline; such comments shall be considered in good faith by the investigator in determining the final form of disclosure. Notwithstanding any of the above, the investigator or others working on the study may not include any confidential information in any such publication or disclosure.

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APPENDIX 1: ECOG PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
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).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX 2: ADULT COMORBIDITY EVALUATION-27

Patient #

P121 - ___ - _____

Date: ___/___/___

Study Staff Signature

Adult Comorbidity Evaluation-27

Identify the important medical comorbidities and grade severity using the index. Overall Comorbidity Score is defined according to the highest ranked single ailment, except in the case where two or more Grade 2 ailments occur in different organ systems. In this situation, the overall comorbidity score should be designated Grade 3.

Cogent comorbid ailment	Grade 3 Severe Decompensation	Grade 2 Moderate Decompensation	Grade 1 Mild Decompensation
Cardiovascular System			
Myocardial Infarct	☐ MI ≤ 6 months	☐ MI > 6 months ago	☐ MI by ECG only, age undetermined
Angina / Coronary Artery Disease	☐ Unstable angina	☐ Chronic exertional angina ☐ Recent (≤ 6 months) Coronary Artery Bypass Graft (CABG) or Percutaneous Transluminal Coronary Angioplasty (PTCA) ☐ Recent (≤ 6 months) coronary stent	☐ ECG or stress test evidence or catheterization evidence of coronary disease without symptoms ☐ Angina pectoris not requiring hospitalization ☐ CABG or PTCA (>6 mos.) ☐ Coronary stent (>6 mos.)
Congestive Heart Failure (CHF)	☐ Hospitalized for CHF within past 6 months ☐ Ejection fraction < 20%	☐ Hospitalized for CHF >6 months prior ☐ CHF with dyspnea which limits activities	☐ CHF with dyspnea which has responded to treatment ☐ Exertional dyspnea ☐ Paroxysmal Nocturnal Dyspnea (PND)
Arrhythmias	☐ Ventricular arrhythmia ≤ 6 months	☐ Ventricular arrhythmia > 6 months ☐ Chronic atrial fibrillation or flutter ☐ Pacemaker	☐ Sick Sinus Syndrome ☐ Supraventricular tachycardia
Hypertension	☐ DBP≥130 mm Hg ☐ Severe malignant papilledema or other eye changes ☐ Encephalopathy	☐ DBP 115-129 mm Hg ☐ DBP 90-114 mm Hg while taking antihypertensive medications ☐ Secondary cardiovascular symptoms: vertigo, epistaxis, headaches	☐ DBP 90-114 mm Hg while not taking antihypertensive medications ☐ DBP <90 mm Hg while taking antihypertensive medications ☐ Hypertension, not otherwise specified
Venous Disease	☐ Recent PE (≤ 6 mos.) ☐ Use of venous filter for PE's	☐ DVT controlled with Coumadin or heparin ☐ Old PE > 6 months	☐ Old DVT no longer treated with Coumadin or Heparin
Peripheral Arterial Disease	☐ Bypass or amputation for gangrene or arterial insufficiency < 6 months ago ☐ Untreated thoracic or abdominal aneurysm (≥6 cm)	☐ Bypass or amputation for gangrene or arterial insufficiency > 6 months ago ☐ Chronic insufficiency	☐ Intermittent claudication ☐ Untreated thoracic or abdominal aneurysm (< 6 cm) ☐ s/p abdominal or thoracic aortic aneurysm repair
Respiratory System			
	☐ Marked pulmonary insufficiency ☐ Restrictive Lung Disease or COPD with dyspnea at rest despite treatment ☐ Chronic supplemental O_2 ☐ CO_2 retention (pCO_2 > 50 torr) ☐ Baseline pO_2 < 50 torr ☐ FEV1 (< 50%)	☐ Restrictive Lung Disease or COPD (chronic bronchitis, emphysema, or asthma) with dyspnea which limits activities ☐ FEV1 (51%-65%)	☐ Restrictive Lung Disease or COPD (chronic bronchitis, emphysema, or asthma) with dyspnea which has responded to treatment ☐ FEV1 (66%-80%)
Gastrointestinal System			
Hepatic	☐ Portal hypertension and/or esophageal bleeding ≤ 6 mos. (Encephalopathy, Ascites, Jaundice with Total Bilirubin > 2)	☐ Chronic hepatitis, cirrhosis, portal hypertension with moderate symptoms "compensated hepatic failure"	☐ Chronic hepatitis or cirrhosis without portal hypertension ☐ Acute hepatitis without cirrhosis ☐ Chronic liver disease manifested on biopsy or persistently elevated bilirubin (>3 mg/dl)
Stomach / Intestine	☐ Recent ulcers(≤ 6 months ago) requiring blood transfusion	☐ Ulcers requiring surgery or transfusion > 6 months ago	☐ Diagnosis of ulcers treated with meds ☐ Chronic malabsorption syndrome ☐ Inflammatory bowel disease (IBD) on meds or h/o with complications and/or surgery
Pancreas	☐ Acute or chronic pancreatitis with major complications (phlegmon, abscess, or pseudocyst)	☐ Uncomplicated acute pancreatitis ☐ Chronic pancreatitis with minor complications (malabsorption, impaired glucose tolerance, or GI bleeding)	☐ Chronic pancreatitis w/o complications

Cogent comorbid ailment	Grade 3 Severe Decompensation	Grade 2 Moderate Decompensation	Grade 1 Mild Decompensation
Renal System			
End-stage renal disease	☐ Creatinine > 3 mg% with multi-organ failure, shock, or sepsis ☐ Acute dialysis	☐ Chronic Renal Insufficiency with creatinine >3 mg% ☐ Chronic dialysis	☐ Chronic Renal Insufficiency with creatinine 2-3 mg%.
Endocrine System	**(Code the comorbid ailments with the (*) in both the Endocrine system and other organ systems if applicable)**		
Diabetes Mellitus	☐ Hospitalization ≤ 6 months for DKA ☐ Diabetes causing end-organ failure ☐ retinopathy ☐ neuropathy ☐ nephropathy* ☐ coronary disease* ☐ peripheral arterial disease*	☐ IDDM without complications ☐ Poorly controlled AODM with oral agents	☐ AODM controlled by oral agents only
Neurological System			
Stroke	☐ Acute stroke with significant neurologic deficit	☐ Old stroke with neurologic residual	☐ Stroke with no residual ☐ Past or recent TIA
Dementia	☐ Severe dementia requiring full support for activities of daily living	☐ Moderate dementia (not completely self-sufficient, needs supervising)	☐ Mild dementia (can take care of self)
Paralysis	☐ Paraplegia or hemiplegia requiring full support for activities of daily living	☐ Paraplegia or hemiplegia requiring wheelchair, able to do some self care	☐ Paraplegia or hemiplegia, ambulatory and providing most of self care
Neuromuscular	☐ MS, Parkinson's, Myasthenia Gravis, or other chronic neuromuscular disorder and requiring full support for activities of daily living	☐ MS, Parkinson's, Myasthenia Gravis, or other chronic neuromuscular disorder, but able to do some self care	☐ MS, Parkinson's, Myasthenia Gravis, or other chronic neuromuscular disorder, but ambulatory and providing most of self care
Psychiatric			
	☐ Recent suicidal attempt ☐ Active schizophrenia	☐ Depression or bipolar disorder uncontrolled ☐ Schizophrenia controlled w/ meds	☐ Depression or bipolar disorder controlled w/ medication
Rheumatologic	**(Incl. Rheumatoid Arthritis, Systemic Lupus, Mixed Connective Tissue Disorder, Polymyositis, Rheumatic Polymyositis)**		
	☐ Connective Tissue Disorder with secondary end-organ failure (renal, cardiac, CNS)	☐ Connective Tissue Disorder on steroids or immunosuppressant medications	☐ Connective Tissue Disorder on NSAIDS or no treatment
Immunological System	**(AIDS should not be considered a comorbidity for Kaposi's Sarcoma or Non-Hodgkin's Lymphoma)**		
AIDS	☐ Fulminant AIDS w/KS, MAI, PCP (AIDS defining illness)	☐ HIV+ with h/o defining illness. $CD4^+ < 200/\mu L$	☐ Asymptomatic HIV+ patient. ☐ HIV^+ w/o h/o AIDS defining illness. $CD4^+ > 200/\mu L$
Malignancy	**(Excluding Cutaneous Basal Cell Ca., Cutaneous SCCA, Carcinoma in-situ, and Intraepithelial Neoplasm)**		
Solid Tumor including melanoma	☐ Uncontrolled cancer ☐ Newly diagnosed but not yet treated ☐ Metastatic solid tumor	☐ Any controlled solid tumor without documented metastases, but initially diagnosed and treated within the last 5 years	☐ Any controlled solid tumor without documented metastases, but initially diagnosed and treated > 5 years ago
Leukemia and Myeloma	☐ Relapse ☐ Disease out of control	☐ 1st remission or new dx <1yr ☐ Chronic suppressive therapy	☐ H/o leukemia or myeloma with last Rx > 1 yr prior
Lymphoma	☐ Relapse	☐ 1st remission or new dx <1yr ☐ Chronic suppressive therapy	☐ H/o lymphoma w/ last Rx >1 yr prior
Substance Abuse	**(Must be accompanied by social, behavioral, or medical complications)**		
Alcohol	☐ Delirium tremens	☐ Active alcohol abuse with social, behavioral, or medical complications	☐ H/o alcohol abuse but not presently drinking
Illicit Drugs	☐ Acute Withdrawal Syndrome	☐ Active substance abuse with social, behavioral, or medical complications	☐ H/o substance abuse but not presently using
Body Weight			
Obesity		☐ Morbid (i.e., BMI ≥ 38)	

OVERALL COMORBIDITY SCORE (Circle one.) **0** None **1** Mild **2** Moderate **3** Severe **9** Unknown

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APPENDIX 3: BRIEF PAIN INVENTORY

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Brief Pain Inventory (Short Form)

Date:____/____/____ Time:_____

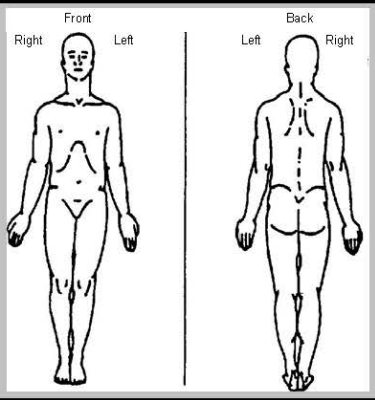
Name:_____ _____ _____

Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

Page 1 of 2

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Date:____/____/____ Time:_____

Name:_____ _____ _____

Last First Middle Initial

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

Page 2 of 2

P12-1 Statistical Analysis Plan was not finalized as there was insufficient data.