**CITY OF HOPE NATIONAL MEDICAL CENTER**
**1500 E. DUARTE ROAD**
**DUARTE, CA 91010**

**DEPARTMENT OF MEDICAL ONCOLOGY AND THERAPEUTICS RESEARCH**

**TITLE:** RANDOMIZED PHASE II TRIAL OF SIPULEUCEL T IMMUNOTHERAPY PRECEDED BY SENSITIZING RADIATION THERAPY AND SIPULEUCEL-T ALONE IN PATIENTS WITH CASTRATE RESISTANT METASTATIC PROSTATE CANCER

**CITY OF HOPE PROTOCOL NUMBER: #12367 VERSION: 09**

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**DISEASE SITE:** PROSTATE CANCER

**STAGE (if applicable):** IV

**MODALITY:** Immunotherapy and Radiation Therapy

**PHASE/TYPE:** II/Randomized

**PRINCIPAL INVESTIGATOR:** Cy Stein M.D.

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**1500 E. DUARTE ROAD**
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| | Amendment 07 | January 24, 2014 |
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**DISEASE SITE:** PROSTATE CANCER

**STAGE (if applicable):** IV

**MODALITY:** Immunotherapy and Radiation Therapy

**PHASE/TYPE:** II/Randomized

**PRINCIPAL INVESTIGATOR:** Cy Stein, M.D.
*Designs protocol, responsible for study conduct and data analysis*

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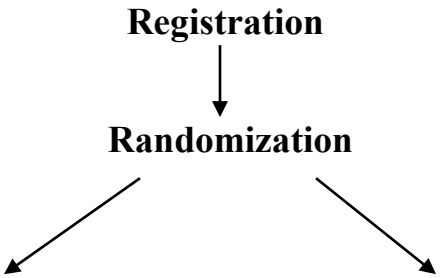
| **DATA COORDINATING CENTER** | City of Hope National Medical Center<br>1500 East Duarte Road<br>Duarte, CA 91010<br>(626) 256-4673 |

## Experimental Design Schema




**Arm A (Sipuleucel-T)** **Arm B (Sipuleucel-T and radiation therapy)**

## Study Schema for Arm A patients: (to simplify comparison between both groups, the start of therapy in group A will be counted as week 3)

| Week 1-2 | Week 3 (Day 19) | Week 4 (Day 22) | Week 5 (Day 33) | Week 6 (Day 36) |
|---|---|---|---|---|
| rest | Sipuleucel-T collection | Sipuleucel-T infusion | Sipuleucel-T collection | Sipuleucel -T infusion |

| Week 7 (Day 47) | Week 8 (Day 50) | Week 4 (Day22), and weeks 12, 24, 36, 48, 60 |
|---|---|---|
| Sipuleucel-T collection | Sipuleucel-T Infusion | Assays for immune correlates |

## Study Schema for Arm B patients:

| Week 1-2 | Week 3 | Week 3 (Day 19) | Week 4 (Day 22) | Week 5 (Day 33) | Week 6 (Day 36) |
|---|---|---|---|---|---|
| EBRT to single met | Rest | Sipuleucel-T collection | Sipuleucel-T infusion | Sipuleucel-T collection | Sipuleucel -T infusion |

| Week 7 (Day 47) | Week 8 (Day 50) | Week 4 (Day22), and weeks 12, 24, 36, 48, 60 |
|---|---|---|
| Sipuleucel-T collection | Sipuleucel-T Infusion | Assays for immune correlates |

# Protocol Synopsis

| **Protocol Title:** |
|---|
| RANDOMIZED PHASE II TRIAL OF SIPULEUCEL T IMMUNOTHERAPY PRECEDED BY SENSITIZING RADIATION THERAPY AND SIPULEUCEL-T ALONE IN PATIENTS WITH CASTRATE RESISTANT METASTATIC PROSTATE CANCER |
| **Brief Protocol Title for the Lay Public (if applicable):** |
| Sipuleucel-T preceded by sensitizing radiation therapy in patients with metastatic castration resistant prostate cancer |
| **Study Phase:** |
| Phase II |
| **Participating Sites:** |
| City of Hope Cancer Center<br>City of Hope South Pasadena<br>Huntsman Cancer Institute, University of Utah |
| **Rationale for this Study:** |
| The combination of radiation therapy and immunotherapy holds promise as a strategy for cancer treatment. Preclinical studies have shown that radiation may act synergistically with immunotherapy to enhance or broaden antitumor immune responses, in part, because of radiation-induced phenotypic alterations of tumor cells that render them more susceptible to immune-mediated killing(1). Clinical trials utilizing the combination of therapeutic vaccines with radiation have supported many of these findings, and other clinical trials are both ongoing and planned. Sipuleucel-T is an active cellular immunotherapy approved for treatment of patients with castrate - resistant, asymptomatic or minimally symptomatic metastatic prostate cancer (2). Our proposal is based on the hypothesis that applying sensitizing radiotherapy to selected metastatic site prior to immunotherapy will enhance immune response in patients treated with Sipuleucel-T. |
| **Objectives:** |
| **Primary Objective**:<br>To assess the feasibility, based on percent able or willing to receive all three infusions of Sipuleucel-T immunotherapy, when combining Sipuleucel-T with radiation therapy to a single site of metastasis delivered one week prior to beginning of Sipuleucel-T therapy<br>**Secondary Objectives:**<br>1. To assess the effect of radiation therapy to single metastasis on immune response (antibody and T-cell proliferation to prostate acid phosphatase PAP and fusion protein PA2024) generated by Sipuleucel-T immunotherapy.<br>2. To assess the effect of external beam radiotherapy to single metastasis on PSA response to therapy with Sipuleucel-T.<br>3. To assess the effect of external beam radiation therapy to single metastasis on radiographic response rate to therapy with Sipuleucel-T.<br>4. To assess the time from the onset of therapy with Sipuleucel-T +/- radiation to the need for subsequent therapy for prostate cancer.<br>5. To assess the toxicity associated with Sipuleucel-T +radiation. |

**Study Design:**

Eligible patients will meet the standard criteria for approved use of Sipuleucel -T. Patients will be randomized to receive standard Sipuleucel-T regimen (Arm A) or Sipuleucel-T preceded by radiation therapy to single site of metastatic disease (Arm B). In patients assigned to Arm B one metastatic site will be selected for radiation based primarily on the safety of radiation in that location. Radiation to bone metastases from L3 down to pelvis and femurs will be excluded provided that patients have other areas of metastases. Patients who have metastases only in the above locations (L3 down to pelvis and femurs) will be allowed provided that they have normal WBC and they will not receive radiation to more than 20% of the bone marrow. Patients will be treated with 300 cGy/day to 3000 cGy. Approximately 7 days after completion of radiation therapy patients will begin therapy with Sipuleucel-T autologous vaccine.

**Endpoints:**

**Primary Endpoint:**

The primary endpoint in this trial will be percent of patients able to receive all three infusions of Sipuleucel-T following radiation therapy. This endpoint reflects both tolerability and the ability to collect adequate numbers of CD54+ cells for the generation of Sipuleucel-T.

**Secondary Endpoint:**

Secondary endpoints will include measurements of immune responses to PAP, PA2024 and PSA and radiologic responses to therapy with Sipuleucel-T +/- external beam radiation therapy to single metastasis. Toxicity comparison between the two arms is also a secondary endpoint.

**Sample Size:**

Total Sample size is 50 randomized in a 1:1 fashion to Arm A and B. Anticipated accrual is 2-3 patients a month.

**Estimated Duration of the Study**

24 months

**Summary of Subject Eligibility Criteria:**

Inclusion Criteria:

Patients with metastatic castration-resistant prostate cancer who are candidates for Sipuleucel-T immunotherapy. Metastatic, minimally symptomatic or asymptomatic disease, ECOG PS 0-2

Exclusion Criteria:

Liver metastases, known brain metastases, > 2 prior chemotherapy regimens

| **Investigational Product Dosage and Administration:** |
| --- |
| Not Applicable. Radiation therapy constitutes investigational component of this study |

| **Clinical Observations and Tests to be Performed:** |
| --- |
| Evaluation for toxicity will be performed at week 4, 6, 8, 12 and every 12 weeks thereafter. PSA will be performed at week 4 and 12, radiologic evaluation will be performed at week 12, and immune assays will be performed at week 4, 12, 24, 36, 48, 60 |
| **Statistical Considerations:** |
| This is a randomized Phase II study. The primary endpoint in this trial will be the ability to safely combine Sipuleucel-T with radiation therapy and collect adequate numbers of CD54+ cells for the generation of Sipuleucel-T. This is measured by the percent of patients able to receive all three infusions of Sipuleucel-T. Secondary endpoints will include toxicity, and measurements of immune responses to PAP, PA2024 and PSA and radiologic responses to therapy with Sipuleucel-T +/- external beam radiation therapy to single metastasis. |
| **Sponsor/Licensee:** |
| City of Hope Cancer Center |
| **Case Report Forms** |
| Not applicable |

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## Abbreviations

| Abbreviation | Meaning |
|---|---|
| AE | Adverse Event |
| CFR | Code of Federal Regulations |
| COH | City of Hope |
| CR | Complete Response |
| CRA | Clinical Research Associate |
| CRF | Case Report Form |
| CRPC | Castration Resistant Prostate Cancer |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTEP | Cancer Therapy Evaluation Program |
| DSMC | Data Safety Monitoring Committee |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| IB | Investigator Brochure |
| ICF | Informed Consent Form |
| IDS | Investigational Drug Services |
| IND | Investigational New Drug |
| IRB | Institutional Review Board |
| NCI | National Cancer Institute |
| PD | Progressive Disease |
| PI | Principal Investigator |
| PMT | Protocol Monitoring Team |
| PR | Partial Response |
| SAE | Serious Adverse Event |
| SD | Stable Disease |

# 1.0 Goals and Objectives (Scientific Aims)

**Primary Objective**:

To assess the feasibility, based on percent able or willing to receive all three infusions of Sipuleucel-T immunotherapy, when combining Sipuleucel-T with radiation therapy to a single site of metastasis delivered one week prior to beginning of Sipuleucel-T therapy

**Secondary Objectives:**

1. To assess the effect of radiation therapy to single metastasis on immune response (antibody and T-cell proliferation to prostate acid phosphatase PAP and fusion protein PA2024) generated by Sipuleucel-T immunotherapy.
2. To assess the effect of external beam radiotherapy to single metastasis on PSA response to therapy with Sipuleucel-T.
3. To assess the effect of external beam radiation therapy to single metastasis on radiographic response rate to therapy with Sipuleucel-T.
4. To assess the time from the onset of therapy with Sipuleucel-T +/- radiation to the need for subsequent therapy for prostate cancer.
5. To assess the toxicity associated with Sipuleucel-T +radiation.

# 2.0 Background

## 2.1 Introduction/Rationale for Development

Prostate cancer is the most common noncutaneous malignancy and the second leading cause of cancer-related death in men in the United States[1]. Androgen deprivation therapy is effective in the initial management of advanced prostate cancer but eventually cancer evolves into the aggressive phenotype referred to as castration resistant prostate cancer (CRPC) which is usually fatal within 12-22 months[2].

Sipuleucel-T is an active cellular immunotherapy consisting of autologous, peripheral blood mononuclear cells (PBMC's), including antigen presenting cells (APC's) that have been activated in vivo with a recombinant fusion protein (PA2024). PA2024 consists of a prostate antigen, prostatic acid phosphatase (PAP) that is fused to granulocyte-macrophage colony-stimulating factor (GMCSF), an immune cell activator[3].

Sipuleucel-T was evaluated in a randomized placebo-controlled Phase III trial in patients with asymptomatic and minimally symptomatic CRPC and demonstrated statistically significant survival advantage of 4.1 months[4]. Main eligibility criteria included the presence of metastatic CRPC, lack of visceral metastases, and lack of significant pain defined by the use of narcotic analgesics. The compound was well-tolerated with brief febrile infusion reactions constituting the main side effect. Sipuleucel-T did not induce significant PSA or objective responses but there was evidence of immune activation targeting prostate antigens. Specifically titers against PA2024 that exceeded 400 at any time after baseline were observed in 66.2 % of patients in the Sipuleucel-T and 2.9% in the placebo group. Patients with positive antibody titer against PA2024 had improved survival as compared to patients who did not generate such response. Antibodies against PAP were observed in 28.5% of patients treated with Sipuleucel-T and 1.4 % in patients in a placebo group. At week 6 , T-cell proliferation responses (stimulation index>5) to PA2024 were seen in 73% of patients in the Sipuleucel-T group and 12.1% in the placebo arm. Responses to PAP were observed in 27.3 % in the Sipuleucel-T group and 8.0% in the placebo group. Based on the results of this trial Sipuleucel-T was approved by Food and Drug Administration for the treatment of patients with metastatic CRPC.

The combination of radiation therapy and immunotherapy holds promise as a strategy for cancer treatment. Preclinical studies have shown that radiation may act synergistically with immunotherapy to

enhance or broaden antitumor immune responses, in part, because of radiation-induced phenotypic alterations of tumor cells that render them more susceptible to immune-mediated killing. Our internal City of Hope data indicates synergistic effect of immunotherapy and radiation in murine model utilizing anti-CEA antibody (Dr Raubitschek-personnel communication.) Clinical trials utilizing the combination of therapeutic vaccines with radiation have supported many of these findings, and other clinical trials are both ongoing and planned. Our proposal is based on the hypothesis that applying sensitizing radiotherapy to selected metastatic site prior to immunotherapy will enhance immune response in patients treated with Sipuleucel-T.

## 2.2 Overview of Proposed Study

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements. Sipuleucel-T (APC8015, Provenge®) is an autologous cell product consisting of antigen presenting cells (APCs) loaded with prostate antigen PA2024, a recombinant fusion protein composed of prostatic acid phosphatase (PAP) linked to granulocyte-macrophage colony-stimulating factor (GM-CSF). GM-CSF acts as a targeting molecule that directs the PAP antigen to APCs and promotes antigen uptake and processing. A dose of sipuleucel-T is prepared from cells from a single leukapheresis procedure, with a minimum of 20 million CD54+ cells (the biologically active component of sipuleucel-T), which is administered via a single intravenous infusion at Weeks 0, 2, and 4. Sipuleucel-T has been approved based on the demonstration of 4.1 months survival advantaged when applied to patients with asymptomatic or minimally symptomatic CRPC. Eligible patients will meet the standard criteria for approved use of Sipuleucel -T. Patients will be randomized to receive standard Sipuleucel-T regimen (Arm A) or Sipuleucel-T preceded by radiation therapy to single site of metastatic disease (Arm B). In patients assigned to Arm B, one metastatic site will be selected for radiation based primarily on the safety of radiation in that location. Radiation to bone metastases from L3 down to pelvis and femurs will be excluded provided that patients have other areas of metastases. Patients who have metastases only in the above locations (L3 down to pelvis and femurs) will be allowed provided that they have normal WBC and they will not receive radiation to more than 20% of the bone marrow. Patients will be treated with following fractionation schemes: 1) 300 cGy/day to 3000 cGy. Approximately 7 days after completion of radiation therapy, patients will begin therapy with Sipuleucel-T autologous vaccine.

## 2.3 Preclinical Studies

Sipuleucel-T-Pre-clinical studies in rats demonstrated that APCs loaded with a fusion protein consisting of rat prostatic acid phosphatase (rPAP) coupled to a targeting molecule, rat granulocyte-macrophage colony-stimulating factor (rGM-CSF), induced strong cellular immune responses in vivo to tissues and tumors that express PAP (Laus 2001). Based on these observations, an APC product, designated APC8015 (sipuleucel-T), was developed for the treatment of men with prostate cancer

## 2.4 Human Studies

Sipuleucel-T Separate Phase 1 and Phase 2 trials of sipuleucel-T were performed at the University of California, San Francisco (UCSF) (Small 2000) and the Mayo Clinic (Burch 2000, Burch 2004). Data from the Phase 1 and Phase 2 trials demonstrated that intravenous infusions of sipuleucel-T were generally well tolerated and effectively stimulated T cell responses to the immunogen. In addition, following therapy with sipuleucel-T, several subjects had decreases in PSA levels or objective tumor regressions suggesting anti-tumor activity. A dose of 3 million CD54+ cells was adequate to generate an immune response. There were no apparent dose related or dose limiting toxicities, warranting the conclusion that the maximum cell dose that could be manufactured from a single leukapheresis product was safe. PR-0292.08, 03 JAN 2008 Page 14 of 55 Dendreon Corporation Sipuleucel-T (APC8015)

A randomized, placebo-controlled, Phase 3 trial (D9901, n = 127 subjects) was subsequently conducted. A statistically significant survival benefit was demonstrated, with the relative risk of death 70% greater for subjects randomized to placebo ($P = 0.010$, 2-sided log rank; HR = 1.71). The median survival was 25.9 months for subjects randomized to sipuleucel-T compared to 21.4 months for those randomized to placebo. At 36 months from randomization, the survival rate for subjects receiving sipuleucel-T was 3.1 times higher than the survival rate for subjects receiving placebo (34% vs. 11%; $P = 0.0046$, chi square) (Small 2006). In addition, when the Kaplan-Meier curves for time to disease progression were compared, there was a delay in the time from randomization to disease progression in the sipuleucel-T group compared with the placebo group (HR = 1.45 [95% CI: 0.99, 2.11], $P = 0.052$). A second smaller, randomized, placebo-controlled Phase 3 trial (D9902A, n = 98 subjects) with the same design as D9901 demonstrated a 20% improvement in median survival for subjects who were randomized to receive sipuleucel-T compared to placebo. Furthermore, at the 3-year follow-up, the percentage of subjects alive in the sipuleucel-T treated group was substantially greater than the percentage of subjects alive who received placebo. The results from this study did not reach statistical significance based on the log rank test. A secondary analysis using a Cox multivariable regression analysis of overall survival, which adjusted for prognostic factors known to influence survival, met the criteria for statistical significance. The HR observed in this Cox multivariable regression analysis was similar to that seen using the same analysis in D9901. The overall AE profile observed in Phase 3 studies (D9901 and D9902A) was similar to that observed in the Phase 2 studies, although infusion-related fevers and rigors appeared to be more common. The following infusion-related AEs occurred more frequently ($P \leq 0.05$) in subjects treated with sipuleucel-T than those treated with placebo: chills, pyrexia, headache, asthenia, dyspnea, vomiting, and tremor. However, these events generally resolved within 1 to 2 days.

Sipuleucel-T was subsequently evaluated in a randomized placebo-controlled Phase III trial in patients with asymptomatic and minimally symptomatic CRPC (IMPACT Trial) and demonstrated statistically significant survival advantage of 4.1 months. Main eligibility criteria included the presence of metastatic CRPC, lack of visceral metastases, and lack of significant pain defined by the use of narcotic analgesics. The compound was well-tolerated with brief febrile infusion reactions constituting the main side effect. Sipuleucel-T did not induce significant PSA or objective responses but there was evidence of immune activation targeting prostate antigens. Specifically titers against PA2024 that exceeded 400 at any time after baseline were observed in 66.2 % of patients in the Sipuleucel-T and 2.9% in the placebo group. Patients with positive antibody titer against PA2024 had improved survival as compared to patients who did not generate such response. Antibodies against PAP were observed in 28.5% of patients treated with Sipuleucel-T and 1.4 % in patients in a placebo group. At week 6, T-cell proliferation responses (stimulation index>5) to PA2024 were seen in 73% of patients in the Sipuleucel-T group and 12.1% in the placebo arm. Responses to PAP were observed in 27.3 % in the Sipuleucel-T group and 8.0% in the placebo group. Based on the results of this trial Sipuleucel-T was approved by Food and Drug Administration for the treatment of patients with metastatic CRPC.

### 2.5 STAT3-Activity

STAT3 activity in tumor-associate myeloid cells is known to orchestrate tumor angiogenesis (Kujawski JCI 2008). Our recent studies assessed whether STAT3 activity in the tumor microenvironment can limit the antitumor effect of the local tumor irradiation. We observed that tumor irradiation can enhance, rather than interrupt, STAT3-mediated crosstalk between cancer and myeloid immune cells. The radiation-induced cell death led to release of endogenous TLR agonists for TLR9, including mitochondrial DNA (mtDNA), which in turn sustain high STAT3 activity in myeloid cells. We demonstrated that STAT3 activation post-irradiation is mostly TLR9-mediated and depends on rapid expression of cytokines inducing Jak/STAT3 signaling, such as IL-6. Cancer cell repopulation was significantly delayed in TLR9-deficient mice compared to wild-type animals, which correlated with reduced STAT3 activation in tumor-infiltrating myeloid cells and impaired reconstitution of tumor blood vessels. In addition, lack of TLR9

expression correlated also with decreased numbers of lung metastases suggesting the role of TLR9 signaling in tumor dissemination. We further verified the negative role of STAT3 for the efficacy of radiation therapy using conditional STAT3 gene deletion in myeloid cells as well as STAT3 silencing using CpG-STAT3siRNA. Both approaches confirmed that elimination of tumorigenic TLR9/STAT3 signaling axis in tumor-associated myeloid cells prevents cancer recurrence following the local tumor irradiation. Targeting STAT3 using immune cell-specific CpG-siRNA strategy is likely to provide a future therapeutic approach to support cancer radiotherapy. In this study we will perform the exploratory analysis of the effect of radiation therapy on the levels of pSTAT3 in Peripheral Blood Mononuclear Cells (PBMCs) and serum levels of proinflammatory cytokines and TLR9 ligands.

# 3.0 Patient Eligibility

Prior to the initiation of screening procedures, the purpose and procedures of the study will be explained to each subject, and each subject will then sign an Institutional Review Board (IRB) approved consent form. The subject will subsequently undergo screening assessments to determine if he meets the eligibility criteria for the study.

## 3.1 Inclusion Criteria

3.1.1. Histologically documented adenocarcinoma of the prostate.

3.1.2. Men at least 18 years of age and life expectancy of ≥ 6 months, ECOG performance status ≤ 2.

3.1.3 Metastatic disease as evidenced by soft tissue and/or bony metastases on baseline bone scan and/or computed tomography (CT) scan or MRI of the abdomen and pelvis.

3.1.4 Castration resistant prostatic adenocarcinoma. Subjects must have current or historical evidence of disease progression despite castrated level of testosterone (< 50 ng/dL) achieved by orchiectomy or LHRH agonist or antagonist therapy. Disease progression has to be demonstrated by PSA progression OR progression of measurable disease OR progression of non-measurable disease as defined below:

3.1.4.1 PSA: Two consecutive rising PSA values, at least 7 days apart.

3.1.4.2 Measurable disease: ≥ 20% increase in the sum of the longest diameters of all measurable lesions or the development of any new lesions. The change will be measured against the best response to castration therapy or against the pre-castration measurements if there was no response.

3.1.4.3 Non-measurable disease

3.1.4.3.1 Soft tissue disease: The appearance of 1 or more new lesions, and/or unequivocal worsening of non-measurable disease when compared to imaging studies acquired during castration therapy or against the pre-castration studies if there was no response.

3.1.4.3.2 Bone disease: Appearance of 2 or more new areas of abnormal uptake on bone scan when compared to imaging studies acquired during castration therapy or against the pre-castration studies if there was no response. Increased uptake of pre-existing lesions on bone scan does not constitute progression.

3.1.5 Following criteria are suggested guidelines and exceptions will be allowed at the discretion of Principal Investigator. Transfusion of blood products are not allowed to normalize blood parameters. Please see the Study Calendar (10.0) for details of the timing of required tests.Adequate hematologic, renal, and liver function as evidenced by the following

White blood cell (WBC) ≥ 2,500 cells/μL

Absolute neutrophil count (ANC) ≥ 1,000 cells/μL
Platelet Count ≥ 75,000 cells/μL
Hemoglobin (HgB) ≥ 9.0 g/dL
Creatinine ≤ 2.5 mg/dL
Total Bilirubin ≤ 2 x institutional upper limit of normal (ULN)
Aspartate aminotransaminase (AST, SGOT) ≤ 2.5 x institutional ULN
Alanine aminotransaminase (ALT, SGPT) ≤ 2.5 x institutional ULN

3.1.6. Prior chemotherapy with 0-2 regimens is allowed.

3.1.7. Prior radiation therapy to prostate or prostate bed is allowed provided it occurred > 3 months before enrollment to the study.

**3.2 Exclusion Criteria**

3.2.1 The presence of liver, or known brain metastases, malignant pleural effusions, or malignant ascites.

3.2.2 Moderate or severe symptomatic metastatic disease defined as a requirement for treatment with opioid analgesics for cancer-related pain within 21 days prior to registration.

3.2.3 Eastern Cooperative Oncology Group (ECOG) performance status > 2 (see Appendix 1).

3.2.4 Treatment with chemotherapy within 3 months of registration.

3.2.5 Treatment with any of the following medications or interventions within 28 days of registration:

- Systemic corticosteroids. Use of inhaled, intranasal, and topical steroids is acceptable.
- Any other systemic therapy for prostate cancer (except for medical castration).

3.2.6 History of external beam radiation therapy to metastatic sites within 1 year of enrollment to the study.

3.2.7 Participation in any previous study involving sipuleucel-T.

3.2.8 Pathologic long-bone fractures, imminent pathologic long-bone fracture (cortical erosion on radiography > 50%) or spinal cord compression.

3.2.9 Concurrent other malignancy with the exception of: a) cutaneous squamous cell and basal carcinomas, b) adequately treated stage 1-2 malignancy , c) adequately treated stage 3-4 malignancy that has been in remission for ≥ 2 years at the time of registration.

3.2.10 A requirement for systemic immunosuppressive therapy for any reason.

3.2.11 Any infection requiring parenteral antibiotic therapy or causing fever (temperature > 100.5°F or 38.1°C) within 1 week prior to registration.

3.2.12 Any medical intervention or other condition which, in the opinion of the Principal Investigator could compromise adherence with study requirements or otherwise compromise the study's objectives.

**3.3 Inclusion of Women and Minorities**

Prostate cancer is exclusively disease of men. The study is open anyone regardless of race and ethnicity. Efforts will be made to extend the accrual to a representative population, but in a trial which will accrue approximately 50 subjects, a balance must be struck between subject safety considerations and limitations on the number of individuals exposed to potentially toxic or ineffective treatments on the one hand and the need to explore racial, and ethnic aspects of clinical research on the other. If differences in outcome that correlate to racial or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

# 4.0 Screening and Registration Procedures

## 4.1 Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial will be done only after obtaining written informed consent. Studies or procedures that were for clinical indications (not exclusively to determine study eligibility) may be used for baseline values, even if the studies were done before informed consent was obtained. Reference is made to Section 10.0 – Study Calendar.

## 4.2 Informed Consent

The investigational nature and objectives of the trial, the procedures and treatments involved and their attendant risks and discomforts, and potential alternative therapies will be carefully explained to the subject and a signed informed consent will be obtained. Documentation of informed consent for screening will be maintained in the subject's research chart and medical record.

## 4.3 Registration Requirements/Process

**Registration Process** To register a patient, the treating physician should contact the protocol nurse or the responsible Clinical Research Associate (CRA) in Clinical Trial Office (CTO) to complete the eligibility/registration form. The protocol nurse or CRA will contact the Data Coordinating Center at the City of Hope (626-256-4673, ext. 64267 or e-mail dcc@coh.org), EMAIL a copy of the completed eligibility checklist, required pre-study tests (per protocol – and may include laboratory, CT and pathology reports), signed Informed Consent, signed Patients' Bill of Rights and HIPAA authorization form to dcc@coh.org.

The patient registration process will be handled by the Department of Information Support (CRIS) Data Coordinating Center (DCC) at City of Hope. current IRB approval must be on file with the DCC prior to registration of for participating institution.

Clinical Research Documentation of patients on this study

The steps below are to be taken when registering a **patient:**

- The research staff must assure they have the most current and updated version of the protocol and informed consent prior to enrolling a patient. If a question arises, please contact the Data Coordinating Center at 626-256-4673 extension 64267 or via email at dcc@coh.org.
- The study staff must assure that all prestudy laboratory tests, scans and x-rays have been completed prior to registration according to the study calendar
- The study staff must assure that the patient has signed an approved informed consent prior to registration/randomization, including the Experimental Subject Bill of Rights and appropriate HIPAA authorization.
- The study staff must confirm that the patient meets all inclusion and exclusion eligibility criteria for the protocol. The eligibility checklist (provided by the COH DCC) must be completed in its entirety.
- Patients must be registered prior to initiation of treatment but no more than 2 weeks prior to planned start of treatment. A patient failing to meet all protocol requirements may not be registered.
- Once a patient is eligible, all the pre-study requirements have been fulfilled, and the informed consent obtained, the research nurse or the data manager (study coordinator) will inform the

COH Data Coordinating Center at (626) 256-4673, extension 64267; email dcc@coh.org and FAX (fax number 626 256-8794) a copy of the patient's signed informed consent, , completed eligibility checklist and corresponding source documentation confirming eligibility (including pathology reports, lab reports, x-ray reports, etc.).

**The City of Hope Data Coordinating Center will:**

- Review all materials/source documentation to ensure the patient is eligible.
- Ensure the consent form is valid and is signed correctly by all parties. If additional information is needed or should there be any questions, the Data Coordinating Center will immediately contact the participating institution and registration will not occur until all issues are resolved.
- If there are questions regarding exceptions to the eligibility criteria, please contact he study Principal Investigator, as well as the COH DCC. Documentation of IRB approval of exception will need to be submitted as well as the COH DCC.
- The patient will be registered and randomized centrally at City of Hope.
- Confirmation of Registration/Randomization will be emailed/faxed to the study staff noting the patient's study number as well as assigning the randomization arm within 24 hours post receipt of a complete eligibility packet.
- The COH DCC will call the research nurse or data manager (study coordinator) and verbally confirm the registration (if needed).
- If the patient does not receive protocol therapy following registration, the patient's registration on the study may be cancelled. The COH DCC should be notified of cancellations as soon as possible.
- The COH DCC will log into the Electronic Data Capture (EDC) system and enter the patient's study number.

### 4.4 Randomization

Randomization will be performed by the Department of Biostatistics

## 5.0 Treatment Program

### 5.1 Treatment Overview

Treatment will be performed on an outpatient basis. Patients randomized to Arm A will we treated with standard Sipuleucel - T. Leukapheresis will be performed at the contracted, designated Dendreon facility and Sipuleucel-T infusion will be performed at the City of Hope infusion clinic approximately 72 hours after leukapheresis. This process will be repeated every 2 weeks times three. Patients randomized to Arm B will undergo 2 weeks of radiation therapy to single metastatic site followed by 7 days of rest followed by treatment with Sipuleucel- T on an identical schedule as Arm A (see study schema) Delays in leukapheresis of up to 2 weeks for each cycle are acceptable regardless of cause.

For a tabular view of the treatment, monitoring, and follow-up schedule, see study calendar in Section 10.

### 5.2 Planned Duration of Therapy

5.2.1 Therapeutic portion of the protocol will last 6 weeks for Arm A patients, and 8 weeks for Arm B patients.

5.2.2 Criteria for Removal from Treatment

Treatment may continue until one of the following criteria applies:

- Completion of 3 courses of Sipuleucel-T
- Symptomatic disease progression
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study,
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Treatment delays of > 2 weeks due to adverse events.
- Patient's preference

### 5.3 Subject Follow-Up

Following completion of therapy patients will be followed clinically and will undergo periodic laboratory and radiographic tests until week 60 or until disease progression requiring additional therapy (see Study calendar 10.0)

### 5.4 Supportive Care, Other Concomitant Therapy, Prohibited Medications

Approximately 30 minutes prior to infusion of Sipuleucel-T subjects must be premedicated with acetaminophen (650 mg) and an antihistamine such as diphenhydramine (Benadryl®, 50 mg). Common treatment-related AEs such as pyrexia and/or rigors may warrant reduction of the infusion rate. If such adverse reactions occur, subsequent infusions should be administered over the shortest period, not less than 60 minutes, that is well tolerated. Subjects must be observed for at least 30 minutes after the infusion. No corticosteroids are to be used for the management of common infusion related AEs. Subjects should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, etc., when appropriate.

### 5.5 Additional Studies

Please see Section 9.0 for the description of correlative studies

## 6.0 Dose Delays/Modifications for Adverse Events

This study will use Common Terminology Criteria for Adverse Events v 4, which can be found at the CTEP, website: http://ctep.cancer.gov/reporting/ctc.html

Management of Anticipated Toxicities: Missed doses of radiation therapy and Sipuleucel -T will not be made up. Treatment should be stopped for any protocol treatment related Grade 3 toxicity or greater that cannot be controlled with good medical practice intervention. Treatment may be resumed upon resolution of that toxicity to Grade 2. A patient who experiences a Grade 3 or higher toxicity again will be removed from the study. There are no provisions for dose reductions of radiation therapy or Sipuleucel-T. The maximum delay in treatment will be 14 days. Patients who received at least one infusion of Sipuleucel-T

will not be replaced. Patients who received at least 50 % of anticipated dose of radiation therapy will not be replaced. Patients who received <50 % of anticipated dose of radiation therapy and / or who did not receive any infusions of Sipuleucel-T will be replaced.

# 7.0 Data and Safety Monitoring, Unanticipated Problems and Adverse Event Reporting

## 7.1 Definition of Risk Level

This is a Risk Level 3 study, as defined in the "City of Hope Data and Safety Monitoring Plan", http://www.coh.org/dsmc/Pages/forms-and-procedures.aspx because it is a Phase II clinical trial where the risks are at least balanced by the potential benefit to subjects and the importance of the knowledge that may result.

## 7.2 Monitoring and Personnel Responsible for Monitoring

The Protocol Management Team (PMT) consisting of the PI, Collaborating Investigator, CRA, protocol nurse, and statistician are responsible for monitoring the data and safety of this study, including implementation of any stopping rules for safety and efficacy.

**Table 1: City of Hope PMT Reporting Timelines for the DSMC**

| Risk Level | Phase | Standard Reporting Requirement |
|---|---|---|
| RL 1, RL2, and Compassionate Use Studies | No reports required | |
| 3 | I | Every 3 months from activation date, as indicated in MIDAS |
| 3 | Pilot, Feasibility, II-IV | Every 6 months from activation date, as indicated in MIDAS |
| 4 | Pilot, Feasibility, I-IV | Every 3 months from activation date, as indicated in MIDAS |

Data and safety will be reported to the COH DSMC using the PMT report and submitted according to the timelines in Table 1 above. Protocol specific data collection will include the following items: summary of accrual, adverse events and treatment-related mortality.

## 7.3 Definitions

**Adverse event (AE)** - An adverse event is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention.

**Unexpected Adverse Event [21 CFR 312.32 (a)** – An adverse event is unexpected if it is not listed in the investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

**Expected Adverse Event** - Any event that does not meet the criteria for an unexpected event OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

**Serious Adverse Event (SAE) [21 CFR 312.32]** is defined as any expected or unexpected adverse event that results in any of the following outcomes:

- Death
- Is life-threatening experience (places the subject at immediate risk of death from the event as it occurred)
- Unplanned hospitalization (equal to or greater than 24 hours) or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Secondary Malignancy
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasisas of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

**Unanticipated problem (UP) – Any incident, experience, or outcome that meets all three of the following criteria:**

1. Unexpected (in term nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; **AND**
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); **AND**
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

### 7.4 Reporting of Unanticipated Problems and Adverse Events

**Unanticipated Problems:** Most unanticipated problems must be reported to the COH DSMC and IRB **within 5 calendar days** according to definitions and guidelines at http://www.coh.org/hrpp/Pages/hrpp-policies.aspx. Any unanticipated problem that occurs during the study conduct will be reported to the DSMC and IRB by submitting electronically in iRIS (http://iris.coh.org).

**Serious Adverse Events -** All SAEs occurring during this study, whether observed by the physician, nurse, or reported by the patient, will be reported according to definitions and guidelines at http://www.coh.org/hrpp/Pages/hrpp-policies.aspx and Table 2 below. Those SAEs that require expedited reporting will be submitted electronically in iRIS (http://iris.coh.org/).

**Adverse Events -** Adverse events will be monitored by the PMT. Adverse events that do not meet the criteria of serious OR are not unanticipated problems will be reported only in the protocol continuation reports and PMT report (see Table 2 below).

**Table 2: City of Hope Adverse Event and Unanticipated Problem Reporting Timelines for the DSMC and IRB**

**Required Reporting Timelines to DSMC for AE/SAEs**
***Investigator Initiated Studies***

| **Required Reporting Timeframe to DSMC** | | |
|---|---|---|
| **Attribution** | **UNEXPECTED** | **EXPECTED** |
| | **Death while on active treatment or within 30 days of last day of treatment** | |
| Possibly, Probably, Definitely | 5 calendar days | |
| Unlikely, Unrelated | | |
| | **Death after 30 days of last active treatment/therapy** | |
| Possibly, Probably, Definitely | 5 calendar days | No reporting required |
| Unlikely, Unrelated | No reporting required | No reporting required |
| | **Grades 3 and 4 AND meeting the definition of "serious"** | |
| Possibly, Probably, Definitely | 5 calendar days | 10 calendar days |
| Unlikely, Unrelated | 5 calendar days | 10 calendar days |
| | **Grades 1 and 2 AND resulting in "hospitalization"** | |
| Possibly, Probably, Definitely | 5 calendar days | 10 calendar days |
| Unlikely, Unrelated | 10 calendar days | 10 calendar days |

***Externally Sponsored Studies***

| Required Reporting Timeframe to DSMC | | |
|---|---|---|
| **Attribution** | **UNEXPECTED[1]** | **EXPECTED** |
| | **Death while on active treatment or within 30 days of last day of treatment** | |
| Possibly, Probably, Definitely | No DSMC reporting required - IRB reporting may be necessary | |
| Unlikely, Unrelated | | |
| | **Death after 30 days of last active treatment/therapy** | |
| Possibly, Probably, Definitely | No DSMC reporting required - IRB reporting may be necessary | |
| Unlikely, Unrelated | | |
| | **Grades 3 and 4 AND meeting the definition of "serious"** | |
| Possibly, Probably, Definitely | No DSMC reporting required - IRB reporting may be necessary | |
| Unlikely, Unrelated | | |
| | **Grades 1 and 2** | |
| Possibly, Probably, Definitely | No DSMC reporting required - IRB reporting may be necessary | |

An event determined by the IRB of record to be an Unanticipated Problem (UP) will be communicated to the Investigator and COH DSMC through the COH IRB Operations Director. The DSMC will review the case and make a determination as to whether the study will be suspended, terminated, amended, or allowed to continue without amendment.

| Required Reporting Timeframe to IRB of Record | | |
|---|---|---|
| **Attribution** | **UNEXPECTED** | **EXPECTED** |
| | **Death** | |
| Possibly, Probably, Definitely | 5 calendar days | Annual |
| Unlikely, Unrelated | Annual | Annual |
| | **Grades 3 and 4 AND meeting the definition of a UP** | |
| Possibly, Probably, Definitely | 5 calendar days | Annual |
| Unlikely, Unrelated | Annual | Annual |
| | **Grade 1 and 2 AND meeting the definition of a UP** | |
| Possibly, Probably, Definitely | 5 calendar days | Annual |
| Unlikely, Unrelated | Annual | Annual |

**7.5 Sponsor-Investigator Adverse Event Reporting**

All SAEs that occur from t he signing of the study specific consent through the duration of the post-therapy adverse event collection period must be reported to Dendreon within 24 hours of being made aware of the SAE. Notification can be made via phone or telefacsimile using an SAE Report Form to be provided by Dendreon.

Dendreon Corporation

Attn: Safety Manager

Facsimile: (206) 829-1647

Phone: (206) 219-7189

After Hours: (206) 274-6774

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

7.6 Safety Reporting Requirements and Timelines – Participating Institutions Only

The guideline is to provide a procedure for accurate and timely reporting of serious adverse events (SAEs) from the participating institution to the FDA, to the Principal Investigator (PI) at City of Hope (COH) as well as to Dendreon. The participating institution, participating institution PI and/or study coordinators are responsible for reporting all serious adverse events immediately (within 24 hours after learning of the event) to their local IRB, the PI at City of Hope, the Data Coordinating Center at COH and to Dendreon.

The participating investigator must report each serious adverse event, regardless of attribution, to the Principal Investigator and to Dendreon within 24 hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event.

After review of Section 7.3 and Section 7.4 above, please report to City of Hope all serious adverse events meeting criteria by telephone (to Dr. Przemyslaw Twardowski and the COH DCC) AND immediately send via fax a copy of the following forms as noted below.

**Participating Institution SAE Notification Contact Numbers:**

| | | |
|---|---|---|
| Dr. Przemyslaw Twardowski | Phone: | 626-256-4673, ext. 68218 |
| | Fax: | 626-301-8233 |
| Data Coordinating Center | Phone: | 626-256-4673 x63968 |
| | **Fax:** | **626-301-8422** |

**Dendreon SAE Form (obtain from COH DCC)**

- Fax Dendreon SAE Form as specified by Dendreon within 24 hours (refer to Section 7.5) to (206) 829-1647
- Fax Dendreon SAE Form to City of Hope Data Coordinating Center within 24 hours to (626) 301-8422, **along with:**
    1. Notification of Unanctipated Problem/Adverse Event (Appendix "A"). This is a coversheet for all reports submitted as required.
    2. Participating institutions internal serious adverse event form. This is the form/report that the participating institutions submit to their IRB of record.
    3. Adverse Event/Unanticipated Problem Reporting Form (Appendix "B").

The participating institution will notify their local IRB as per their local established guidelines and include a copy of the completed Dendreon SAE Form.

The Data Coordinating Center at City of Hope will send a copy of the participating institutions serious adverse event (reported via Dendreon SAE Form and institutional SAE report) to the following internal departments:

City of Hope IRB and DSMC (as applicable)

City of Hope Office of IND Development and Regulatory Affairs (as applicable)

Any supporting documentation to the reports (i.e., laboratory, pathology, progress notes, discharge summary, autopsy, etc.) explaining the adverse event should also be submitted to the Data Coordinating Center at City of Hope. The Data Coordinating Center will then submit to our COH IRB/DSMC.

# 8.0 Agent Information and Risks

## 8.1 Sipuleucel –T (Provenge®)

### 8.1.1 Sipuleucel-T overview

Sipuleucel- T (Provenge ®) is commercially available autologous therapeutic cancer vaccine made of recombinant fusion protein consisting of human PAP and GM-CSF. GM-CSF acts as a targeting molecule that directs the PAP antigen to APCs and promotes antigen uptake and processing. PAP is a tissue-specific target antigen rather than a tumor-specific target antigen. Studies with specific monoclonal antibodies and RNA probes indicate that the antigen is strictly prostate-specific. Immunohistochemical studies reveal that the antigen is expressed by normal prostate tissue, and > 90% of all prostatic adenocarcinomas, but is not expressed by other tissues (Goldstein 2002). PAP is secreted by the prostate tumor cells in vivo, and an elevated serum level is found in most subjects with advanced prostate cancer (Kuriyama 1982). The cDNA for PAP has been isolated. Analysis of sequence homology with other known proteins reveals a low risk of cross-reactivity of immune responses. GM-CSF is a multilineage factor that may also activate mature granulocytes and macrophages, and may activate quiescent APCs. Sipuleucel-T is an autologous cell product consisting of APCs loaded with prostate antigen PA2024. Preparation of sipuleucel-T entails isolating quiescent APCs from a subject's peripheral blood leukapheresis product by buoyant density techniques and then culturing them for approximately 2 days in the presence of PA2024. The culture medium does not contain serum or exogenous cytokines. During the culture process, APCs specifically and selectively pick up antigen (PA2024) and differentiate into antigen loaded APCs capable of presenting antigen to T cells. These APCs thus represent the cells responsible for the biological activity of sipuleucel-T. Other cell populations in sipuleucel-T co-purify with APCs during buoyant density centrifugation, but do not incorporate or present antigen, and are therefore referred to as "non-APCs." After the culture period, the cells are washed and suspended in Lactated Ringer's Injection, USP. The final preparation of PA2024-loaded APCs is designated sipuleucel-T. Sipuleucel-T is placed in a refrigerated package and transported to the clinical site for infusion.

### 8.1.2 Leukapheresis and Collection of Quiescent APCs

Leukapheresis and collection of blood cells to generate sipuleucel-T is performed at the facility contracted by the manufacturer Dendreon and is analogous to that for autologous blood transfusions. Briefly, subjects undergo a standard 1.5 to 2.0 blood volume leukapheresis to harvest peripheral blood mononuclear cells (PBMCs; primarily lymphocytes and monocytes). Prior mobilization with a colony-stimulating factor is not performed. Immediately after collection, the leukapheresis product is transported to a regional manufacturing facility

### 8.1.3 Quality Testing

Quality control (QC) testing is performed at several time points during the manufacturing process and on samples of the final product. If the final product passes all required release tests, an approval to infuse the product (Cell Product Disposition Form) is faxed to the infusion center. If a cell product does not meet Dendreon quality specifications, Dendreon will contact the infusion center by telephone and by fax.

Dendreon will provide instructions for product return or destruction of cell products that are not approved or not infused.

### 8.1.4 Storage and Time Limitations

The infusion of Sipuleucel-T must begin prior to the expiration time indicated on the product label. Expired cell products must not be infused.

### 8.1.5 Administration

The administration of Sipuleucel-T is performed in the City of Hope infusion clinic. Subjects are premedicated with acetaminophen and an antihistamine such as diphenhydramine prior to the infusion. After the site receives the Cell Product Disposition Form indicating the cell product is approved, the infusion is administered over approximately 60 minutes through an intravenous (IV) line suitable for blood transfusion (without a cell filter). Subjects are observed for at least 30 minutes following the infusion.

### 8.1.6 Toxicity

The safety evaluation of Sipuleucel-T is based on 601 prostate cancer patients in the Sipuleucel-T group who underwent at least 1 leukapheresis procedure in four randomized, controlled clinical trials. The control was non-activated autologous peripheral blood mononuclear cells.

Almost all (98.3%) patients in the Sipuleucel-T group and 96.0% in the control group reported an adverse event. The most common adverse events, reported in patients in the Sipuleucel-T group at a rate ≥ 15%, were chills, fatigue, fever, back pain, nausea, joint ache, and headache. In 67.4% of patients in the Sipuleucel-T group, these adverse events were mild or moderate in severity. Severe (Grade 3) and life-threatening (Grade 4) adverse events were reported in 23.6% and 4.0% of patients in the Sipuleucel-T group compared with 25.1% and 3.3% of patients in the control group. Fatal (Grade 5) adverse events were reported in 3.3% of patients in the Sipuleucel-T group compared with 3.6% of patients in the control group. The most common (≥ 2%) Grade 3-5 adverse events reported in the Sipuleucel-T group were back pain and chills.

Serious adverse events were reported in 24.0% of patients in the Sipuleucel-T group and 25.1% of patients in the control group. Serious adverse events in the Sipuleucel-T group included acute infusion reactions, cerebrovascular events, and single case reports of eosinophilia, rhabdomyolysis, myasthenia gravis, myositis, and tumor flare.

Sipuleucel-T was discontinued in 1.5% of patients in Study 1 due to adverse events. Some patients who required central venous catheters for treatment with PROVENGE developed infections, including sepsis. A small number of these patients discontinued treatment as a result. Monitoring for infectious sequelae in patients with central venous catheters is recommended.

Each dose of Sipuleucel-T requires a standard leukapheresis procedure approximately 3 days prior to the infusion. Adverse events that were reported ≤ 1 day following a leukapheresis procedure in ≥ 5% of patients in controlled clinical trials included citrate toxicity (14.2%), oral paresthesia (12.6%), paresthesia (11.4%), and fatigue (8.3%).

Table 1 provides the frequency and severity of adverse events reported in ≥ 5% of patients in the Sipuleucel-T group of randomized, controlled trials of men with prostate cancer.

**Table 1 Incidence of Adverse Events Occurring in ≥ 5% of Patients Randomized to Sipuleucel-T**

| | Sipuleucel-T (N = 601) | | Control* (N = 303) | |
|---|---|---|---|---|
| | All Grades n (%) | Grade 3-5 n (%) | All Grades n (%) | Grade 3-5 n (%) |
| Any Adverse Event | 591 (98.3) | 186 (30.9) | 291 (96.0) | 97 (32.0) |
| Chills | 319 (53.1) | 13 (2.2) | 33 (10.9) | 0 (0.0) |
| Fatigue | 247 (41.1) | 6 (1.0) | 105 (34.7) | 4 (1.3) |
| Fever | 188 (31.3) | 6 (1.0) | 29 (9.6) | 3 (1.0) |
| Back pain | 178 (29.6) | 18 (3.0) | 87 (28.7) | 9 (3.0) |
| Nausea | 129 (21.5) | 3 (0.5) | 45 (14.9) | 0 (0.0) |
| Joint ache | 118 (19.6) | 11 (1.8) | 62 (20.5) | 5 (1.7) |
| Headache | 109 (18.1) | 4 (0.7) | 20 (6.6) | 0 (0.0) |
| Citrate toxicity | 89 (14.8) | 0 (0.0) | 43 (14.2) | 0 (0.0) |
| Paresthesia | 85 (14.1) | 1 (0.2) | 43 (14.2) | 0 (0.0) |
| Vomiting | 80 (13.3) | 2 (0.3) | 23 (7.6) | 0 (0.0) |
| Anemia | 75 (12.5) | 11 (1.8) | 34 (11.2) | 7 (2.3) |
| Constipation | 74 (12.3) | 1 (0.2) | 40 (13.2) | 3 (1.0) |
| Pain | 74 (12.3) | 7 (1.2) | 20 (6.6) | 3 (1.0) |
| Paresthesia oral | 74 (12.3) | 0 (0.0) | 43 (14.2) | 0 (0.0) |
| Pain in extremity | 73 (12.1) | 5 (0.8) | 40 (13.2) | 1 (0.3) |
| Dizziness | 71 (11.8) | 2 (0.3) | 34 (11.2) | 0 (0.0) |
| Muscle ache | 71 (11.8) | 3 (0.5) | 17 (5.6) | 0 (0.0) |
| Asthenia | 65 (10.8) | 6 (1.0) | 20 (6.6) | 2 (0.7) |
| Diarrhea | 60 (10.0) | 1 (0.2) | 34 (11.2) | 3 (1.0) |
| Influenza-like illness | 58 (9.7) | 0 (0.0) | 11 (3.6) | 0 (0.0) |
| Musculoskeletal pain | 54 (9.0) | 3 (0.5) | 31 (10.2) | 3 (1.0) |
| Dyspnea | 52 (8.7) | 11 (1.8) | 14 (4.6) | 3 (1.0) |
| Edema peripheral | 50 (8.3) | 1 (0.2) | 31 (10.2) | 1 (0.3) |
| Hot flush | 49 (8.2) | 2 (0.3) | 29 (9.6) | 1 (0.3) |
| Hematuria | 46 (7.7) | 6 (1.0) | 18 (5.9) | 3 (1.0) |
| Muscle spasms | 46 (7.7) | 2 (0.3) | 17 (5.6) | 0 (0.0) |

## 8.2 Radiation therapy

### 8.2.1 Treatment Plan:

In patients assigned to Arm B one metastatic site will be selected for radiation based primarily on the safety of radiation in that location. Radiation to bone metastases in L3-S5, pelvis and femurs will be excluded provided that patients have other areas of metastases. Patients who have metastases only in the above locations (L3-S5, pelvis and femurs) will be allowed provided that they have normal WBC and they will not receive radiation to more than 20% of the bone marrow. The gross tumor volume (GTV) will be defined as the radiological dimensions of the lesion as identified by CT and/or MRI. The planning tumor volume (PTV) is defined as the GTV plus 1 cm. For lesions that move with respiration (Rib and lung parenchymal lesions for example) CT simulation will be performed at inspiration and expiration to define lesion position during the respiratory cycle. The GTV will be defined based on lesion position during the respiratory cycle. Radiation treatment fields will arranged to minimize dose to the marrow and whole body. Conventional AP/PA technique will be used. Field will be limited to 10 by 10 cm.Patients will be treated with 300 cGy/day to 3000 cGy; Approximately 7 days after completion of radiation therapy, patients will begin therapy with Sipuleucel-T autologous vaccine.

### 8.2.2 Toxicity:

The risks of radiation therapy depend on the part of the body being treated. These side effects are generally mild and expected to resolve 1-2 weeks after radiation is completed:

-fatigue,

-anorexia

-gastroesophageal reflux

-diarrhea

-nausea

-dysuria

-urinary frequency

-pain flare

-skin rash,

-neutropenia,

-thrombocytopenia,

-anemia

Long term effects of radiation also depend on the specific location being treated and include:

- pneumonitis

- cystitis

- hematuria

- secondary malignancy

- chronic diarrhea

- bowel perforation

# 9.0 Correlative/Special Studies

**Blood collection must be scheduled Monday to Thursday to allow for overnight shipping to be received by Friday.** Specimens will be labeled with the subjects research participant number.

## 9.1 Blood Collection

### ALL SUBJECTS

100ml total whole blood (90mL collected in sodium heparin vacutainer tubes and 10mL collected in no-anticoagulant vacutaine tubes- from Becton Dickinson) collected at each time point specified in the study calendar (pre-study, and during weeks 4, 12, 24, 36, 48, and 60) will be sent to:

Send the sample(s) **priority overnight** via FedEx Next Day to:

Dendreon Corporation

Attention: Clinical Immunology

1208 Eastlake Avenue E, Seattle, WA 98102

Phone: 206-829-1639

### ONLY SUBJECTS RECEIVING RADIATION AT CITY OF HOPE

10ml of the whole blood in the BD Vacutainer CPT tube (with Heparin) will collected at baseline (week 0) and at week 4 after radiation to be sent to the laboratory of Dr. Marcin Kortylewski within 4 hours of collection to avoid degradation of the phosphomoieties (i.e., pSTAT3) assessed in this protocol. CPT tubes will be centrifuged at 1800g (approximately 2800 rpm on a Sorvall RT6000 centrifuge) for 20 min. at room temperature. After centrifugation, plasma in the CPT tubes will be gently pipetted against the gel plug to dislodge cells stuck to the top of the gel. The cell suspension will be transferred to a 50 mL conical polypropylene tube. cRPMI will be added to a total of 40 mL. A 10 mL aliquot of cell suspension for counting will be removed. The 50 mL tubes will then be centrifuged at 250g for seven minutes at room temperature. When centrifugation is complete, the supernatant will be aspirated. PMBCs will be either cryopreserved or used fresh.

## 9.2 Immune Assays

### 9.2.1 Cellular immune response assays – Elispot

Antigen-specific memory T cell responses are assayed by means of a IFNγ ELISPOT assay. PVDF ELISPOT (enzyme-linked immunoSPOT) plates (Millipore) are coated with an anti-IFNγ monoclonal antibody (mAb) (clone D1K, MabTech) overnight, after which time plates are blocked and washed with phosphate-buffered saline/Tween (PBST). Cryopreserved PBMC, thawed and rested overnight in medium are then plated in triplicate at $3x10^5$ PBMC/well in a total volume of200µL/well with either medium alone or with medium containing antigen (PA2024: PAP-GMCSF fusion protein, PAP or PHA – Phytohaemagglutinin, an assay control). Plates are then incubated for 40-48 hrs after which time plates are washed then incubated with Strepatavidin conjugated anti-

IFNγ mAb (clone B6-1, MabTech). After incubation plates are further washed with PBST and then incubated biotin conjugated with alkaline peroxidase for a further hour. Afterwards plates are then washed with PBST and then incubated with a substrate, BCIP (5-Bromo-4-chloro-3-indolyl phosphate) to visualize IFNγ secreting cells. ELISPOT data are presented as the median of triplicates with background (PBMCs incubated with media) IFNγ spots subtracted.

#### 9.2.2 Cellular immune response assays – Proliferation

Antigen-specific T cell proliferation to PA2024, PAP and PHA are assayed by means a standard tritiated thymidine ($^3$H-thymidine) incorporation assay using round bottom 96 well tissue culture plates. Cryopreserved PBMC, thawed and rested overnight in medium are then plated in triplicate at $1x10^5$ PBMC/well in a total volume of200μL/well with either medium alone or with medium containing antigen (PA2024: PAP-GMCSF fusion protein, PAP or PHA). Plates are incubated for 5 days, after which the wells are pulsed with 0.5μCi of $^3$H-thymidine overnight, and the amount of $^3$H-thymidine incorporation into the nucleus Is quantified by means of a β-radiation counter with the degree of proliferation expressed as a stimulation index (SI), defined as $^3$H-thymidine incorporation in the presence of antigen divided by $^3$H-thymidine incorporation with media alone.

#### 9.2.3 Humoral response assays

Antibody responses against PA2024 and PAP are determined by means of standard antibody ELISA (enzyme-linked immunosorbent assay). 96 well flat bottomed plates are coated with either PA2024, PAP or Tetanus (an assay control, and measure of immunocompetence) overnight, after which time plates are blocked with PBS/casein and then washed with PBST. Serially diluted serum is then added in duplicate to each set of plates and incubated at room temperature for 2 hours, after which time plates are washed with PBST and then incubated with a mixture of anti-IgM and anti-IgG (Jackson Immunoresearch) for an hour. After this time plates are washed again with PBST and then incubated for an hour with horse radish phosphatase conjugated anti IgG+amti-IgM. Plates were further washed with PBST and O-phenylenediamine dihydrochloride substrate (Sigma) was then added for 15 minutes after which the developing reaction was stopped by the addition of 50 μl/well of 2N HCL (Sigma). Plates were read on a Synergy HT spectrophotometer (BioTEK) at 492 nm and the endpoint titer was determined as being the last dilution of serum that yielded an O.D. reading equivalent to assay background.

### 9.3 Analysis of PBMCs

9.3.1 Analysis of pSTAT3 in PBMCs

Analysis of pSTAT3 will be conducted through previously reported techniques (Kortylewski *et al. Nature Med* 2007). PBMCs will be immersed in a mixture of PBS, 2% FCS and 0.1% (wt/vol) sodium azide with Fc III/IIR-specific antibody to block nonspecific binding and stained the cells with different combinations of fluorochrome-coupled antibodies to CD4, CD14, CD15, CD25, CD33, FoxP3 or HLA-DR as well as 7AAD for dead cell exclusion (BD Biosciences). We collected fluorescence data on

FACSCalibur (Beckton Dickinson) and analyzed them using FlowJo software (Tree Star). This method has been previously published by Chalmin et al.11

### 9.3.2 Determination of serum cytokine and chemokine levels

Serum levels of proinflammatory cytokines and chemokines induced by radiation therapy will be ascertained through the Luminex Protein Assay (Invitrogen) as per manufacturer instructions.

### 9.3.3 Detection of circulating mtDNA and other TLR9 ligands

Levels of TLR9 ligands (e.g. mtDNAs), will be assessed using quantitative qPCR as described by Zhang et al.(Blood 2013). Briefly, DNA will be isolated from plasma samples using QIAamp DNA Mini kit (Qiagen). The presence of human mitochondrial genes, such as cytochrome B, cytochrome C oxidase subunit III and NADH dehydrogenase, will be detected by qPCR using specific pairs of primers on CFX96 thermocycler (Biorad).

# 10.0 Study Calendar

**Table 1 Schedule of Events (time scale in weeks)**

**ARM B [#]**

| | Week [f] | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pre-Study * | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 [b] | Off Study Visit[i] |
| Radiation therapy [#] (Arm B only) | | X | X | | | | | | | | | | | |
| Sipuleucel-T collection | | | | X | | X | | X | | | | | | |
| Sipuleucel-T infusion | | | | | X | | X | | X | | | | | |
| Informed consent | X | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | X |
| Physical exam | X | | | | X | | X | | X | | | | X | X |
| Performance Status | X | | | | X | | X | | X | | | | X | X |
| CBC w/diff, plts | X | X | X | X | | X | | X | | | | | X | Xe |
| Serum chemistry [a] | X | | | | X | | X | | X | | | | X | Xe |
| PSA | X | | | | X | | | | | | | | X | Xe |
| Testosterone | X | | | | | | | | | | | | X | |
| EKG (as indicated) | X | | | | | | | | | | | | | |
| CXR (if no CT chest done) | X | | | | | | | | | | | | X[c] | X[c] |
| Radiologic evaluation(bone scan, CT (Chest[g]) Abd/pelvis [g] | X | | | | | | | | | | | | X[c] | X[c] |
| Tumor measurements | X | | | | | | | | | | | | X[c] | X[c] |
| Adverse event evaluation | | | | | X | | X | | X | | | | X[c] | X[c] |
| Immune Assays | X | | | | X | | | | | | | | X[d] | |
| Analysis of PBMCs[h] | X | | | | X | | | | | | | | | |

Patients on ARM A will not undergo radiation therapy, otherwise they will follow the same schedule as ARM B beginning on week 3

* Prestudy tests should be performed within 28 days of registration

a. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT[AST], SGPT[ALT], sodium.

b. and every 12 weeks thereafter until off the study

c. after week 12 radiologic evaluation and tumor measurement will be done at the discretion of treating physician
d. after week 12 Immune Assays will be performed at following time intervals : week 24, 36, 48, 60
e. Off study visit laboratory tests will b performed at the discretion of treating physician
f. this protocol allows for flexibility of suggested timing of visits and tests : +/- 1 week during first 8 weeks of study and +/- 2 weeks thereafter
g. Chest CT is optional. If not done it can be replaced with PA and LAT Chest XRay. MRI of the abdomen and pelvis can be used instead of CT
h. City of Hope subjects who receive radiation only
i. done approximately 30 days post study completion

# 11.0 Endpoint Evaluation Criteria/Measurement of Effect

## 11.1 Measurability of lesions

a. **Measurable disease**: Lesions that can be accurately measured in at least one dimension by 1) medical photograph (skin or oral lesion), palpation, plain x-ray, CT, MRI or other conventional technique with longest diameter 2 cm or greater in the axial plane (bone lesions not included), or 2) spiral CT with longest diameter 1 cm or greater. Ultrasound is suitable only for superficial disease (superficial palpable nodes, subcutaneous lesions, thyroid nodules).

Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm.

b. **Non-measurable disease**: All other lesions including lesions too small to be considered measurable, pleural or pericardial effusions, ascites, bone disease, inflammatory breast disease, leptomeningeal disease, lymphangitis, pulmonitis, abdominal masses not confirmed and followed by imaging techniques, cystic lesions or disease documented by indirect evidence only (e.g., by lab values), previously radiated lesions that have not progressed.

## 11.2 Objective status

Objective Status is to be recorded at baseline, at week 12 (or at the time of disease progression if it happened earlier than 12 weeks) All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. All measurable lesions not identified as target lesions are non-target lesions and are included as non-measurable disease. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

a. **Complete Response (CR)**: Complete disappearance of all measurable and non-measurable disease. No new lesions. No disease related symptoms, normalization of disease-related abnormal lab values. Normalization of PSA marker to $\leq$.0.2 in patients who had prior prostatectomy. In patients who had primary radiation therapy to prostate gland PSA decrease to < nadir +2. All disease must be assessed using the same technique as baseline.

b. **Partial Response (PR)**: Radiographic PR applies only to patients with at least one measurable lesion. Greater than or equal to 30% decrease under baseline of the sum of longest diameters of all target measurable lesions. No unequivocal progression of non-measurable disease. No new lesions. All target measurable lesions must be assessed using the same techniques as baseline. PSA PR refers to PSA decline by >50% from baseline and confirmed at least 3 weeks later.

c. **Stable**: Does not qualify for CR, PR, Progression or Symptomatic Deterioration. All target measurable lesions must be assessed using the same techniques as baseline.

d. **Progression**: One or more of the following must occur: 20% increase in the sum of longest diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of any new lesion/site. PSA increase by 25 % form baseline or nadir (whichever was smaller) and by $\geq$ 2 ng/mL at 12 weeks. Death due to disease without prior documentation of progression and without symptomatic deterioration.

e. **Symptomatic deterioration**: Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.

f. **Assessment inadequate, objective status unknown**: Progression or symptomatic deterioration has not been documented, and one or more target measurable lesions have not been assessed or inconsistent assessment methods were used.

g. **Objective status notes:**

1. Non-measurable and non-target measurable disease do not affect objective status except in determination of CR (must be absent--a patient who otherwise has a CR, but who has non-measurable or non-target measurable disease present or not assessed, will be classified as having a PR), and in determination of progression (if new sites of disease develop or if unequivocal progression occurs in the opinion of the treating physician).
2. An objective status of PR or stable cannot follow one of CR. Stable can follow PR only in the rare case that tumor increases too little to qualify as progression, but enough that a previously documented 30% decrease no longer holds.
3. In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), objective status is not progression unless either symptoms persist beyond 4 weeks or there is additional evidence of progression.
4. Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.
5. For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression.
6. Appearance or worsening of pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin.
7. If CR determination depends on a lesion for which the status is unclear by the required tests, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate.

# 12.0 Data Reporting/Protocol Deviations

## 12.1 Confidentiality and Storage of Records

The original data collection forms will be stored at the originating institution in a secure location. Study data will be entered into an electronic case report form (eCRF) using an encrypted, password protected, secure electronic data capture (EDC) application that meets all HIPAA requirements. When results of this study are reported in medical journals or at meetings, identification of those taking part will not be disclosed. Medical records of subjects will be securely maintained in the strictest confidence, according to current legal requirements. They will be made available for review, as required by the FDA, HHS, or other authorized users such as the NCI, under the guidelines established by the Federal Privacy Act and rules for the protection of human subjects.

## 12.2 Subject Consent Form

The original signed and dated Informed Consent form, HIPAA research authorization form, and the California Experimental Subject's Bill of Rights will be stored in the research record. At the time of registration, a copy of the original signed and dated consent documents will be available to the patient and another copy will be stored in the medical record. All Institutional, NCI, Federal, and State of California requirements will be fulfilled.

## 12.3 Data Collection Forms and Submission Schedule

All data will be collected using Medidata EDC electronic case report forms.

*12.3.1 Eligibility Checklist*

The Eligibility Checklist must be completed by a protocol nurse or clinical research associate and signed by an authorized investigator prior to registering the subject. See Section 4.3 for the registration procedure.

*12.3.2 Prior Therapy Forms and On-Study Forms*

Within two weeks of registration, the clinical research associate will submit Prior Therapy Forms and On-Study Forms.

*12.3.3 Treatment Forms, Adverse Event Collection Forms, Response/Off Study/Follow Up Forms*

Within four weeks of completion of therapy, the clinical research associate will submit the Treatment Forms. Completed adverse events collection forms are due within four weeks of assessments per study calendar (refer to Section 10.0). Response/Follow Up/Off Study Forms are to be submitted within four weeks of the patient being evaluated for response and/or new follow up information is obtained.

## 12.4 Protocol Deviations

## 12.5 Deviation Policy

This protocol will be conducted in accordance with COH's "Clinical Research Protocol Deviation Policy" located at http://www.coh.org/dsmc/Documents/Institutional%20Deviation%20Policy.pdf.

Deviations from the written protocol that could increase patient risk or alter protocol integrity require prior IRB approval of a single subject exception (SSE) request. In addition, if contractually obligated, the sponsor must also approve the deviation. IRB pre-approved SSE protocol modifications are considered an amendment to the protocol and not a deviation. The submission of a deviation report is not required.

Brief interruptions and delays may occasionally be required due to travel delays, airport closure, inclement weather, family responsibilities, security alerts, government holidays, etc. This can also extend to complications of disease or unrelated medical illnesses not related to disease progression. The PI has the discretion to deviate from the protocol when necessary so long as such deviation does not threaten patient safety or protocol scientific integrity. Examples include, but are not limited to: a) dose adjustments based on excessive patient weight; b) alteration in treatment schedule due to non-availability of the research participant for treatment; c) laboratory test results which are slightly outside the protocol requirements but at levels that do not affect participant safety. These instances are considered to be deviations from the protocol. A deviation report will be submitted to the DSMC/IRB within five days.

12.5.1 Reporting of Deviations

All deviations will be reported to the COH DSMC within five days. The DSMC will forward to report to the IRB following review.

12.5.2 Resolving Disputes

The COH Investigational Drug Service (IDS) cannot release a research agent that would cause a protocol deviation without approval by the PI. Whenever the protocol is ambiguous on a key point, the IDS should rely on the PI to clarify the issue.

In situations where there is misperception or dispute regarding a protocol deviation among the persons involved in implementing the protocol, it is the responsibility of the PI to resolve the dispute and the PI may consult with the DSMC chair (or designee) to arrive at resolution.

# 13.0 Statistical Considerations

## 13.1 Study Design

This is a randomized Phase II study. The primary endpoint is to assess the feasibility, based on percent able or willing to receive all three infusions of Sipuleucel-T immunotherapy, when combining Sipuleucel-T with radiation therapy to a single site of metastasis delivered one week prior to beginning of Sipuleucel-T therapy. The ability to deliver three infusions of Sipuleucel-T, reflects the ability to collect adequate numbers of CD54+ cells for the generation of Sipuleucel-T, and tolerability reflected in the patient's willingness or ability to receive the three infusions. Secondary endpoints will include toxicity, and measurements of immune responses to PAP, PA2024 and PSA and radiologic responses to therapy with Sipuleucel-T +/- external beam radiation therapy to single metastasis.

## 13.2 Sample Size Accrual Rate

Patients with metastatic castration-resistant prostate cancer who are candidates for Sipuleucel-T immunotherapy. Total Sample size 50. Anticipated accrual is 2-3 patients a month. Likely duration of the study is 2 years. Randomization is 1:1.

## 13.3 Statistical Analysis Plan

Primary Endpoint: Previous publications suggest 8% were unable or unwilling to receive all three infusions of Sipuleucel-T. We will stop accrual at any time if more than 2 patients are unable to receive all three infusions and more than 30% of the patients are unable to receive all three infusions. This rule has a 4% of stopping if 8% are unable or unwilling to receive all three infusions, and a 82% chance of stopping early if 33% are unable or unwilling to receive all three infusions (based on 1000 simulations). In addition, if 3 patients in the first 10 are unable to initiate Sipulecel-T immunotherapy on Arm B, the study will hold accrual pending review by the COH DSMB, sponsor and PI. This slightly increase the chance of early stopping (3 of 10 is not "more than 30%" but equal to 30%). Previous publications suggest only 2% of patients are unwilling or unable to begin Sipuleucel-T immunotherapy.

In addition, to the above stopping boundaries, there will be a safety review of the toxicities after 10 patients have been treated on Arm B, or after any grade 3 or higher treatment related toxicity on Arm B. These rules are in place to limit patient exposure to arm B if it proves poorly tolerated or too toxic.

Secondary Endpoint:

From the IMPACT study, titers of antibodies against prostatic acid phosphatase exceeded 400 in 28.5% of the patients treated with Sipuleucel-T. By having a control group, a Fisher's exact test with a 0.200 one-sided significance level will have 86% power to detect the difference between non-radiation proportion, 0.285 and a radiation-treated group proportion of 0.570 when the sample size in each group is 25. Also, with 25 patients, if the true proportion about 400 is 28.5% in the control arm, and 48.5% in the radiation arm, there is less than a 5% chance (~1% if the radiation proportion is 57%) that the observed proportion will be higher in the control arm, and there is an 85% chance that difference will exceed 8% between the two arms. In addition, secondary endpoints will include measurements of immune responses to PA2024 and PSA and radiologic responses to therapy with Sipuleucel-T +/- external beam radiation therapy to single metastasis.

As a result, by having a concurrently randomized control arm, initial comparisons of Arm A and Arm B including the influence of radiation on PSA kinetics and response, toxicity and tolerability will help

motivate future studies. For this exploratory secondary analysis, we will not include patients (if any) who do not start Sipuleucel-T immunotherapy, but will include all patients who start. A subset analysis of patients able to complete the planned three infusions will also be conducted.

# 14.0 Human Subject Issues

## 14.1 Institutional Review Board

In accordance with City of Hope policies, an Institutional Review Board (IRB) that complies with the federal regulations at 45 CFR 46 and 21 CFR 50, 56 and State of California Health and Safety code, Title 17, must review and approve this protocol and the informed consent form prior to initiation of the study. All institutional, NCI, Federal, and State of California regulations must be fulfilled.

## 14.2 Recruitment of Subjects

Patients for the study with will be recruited from patients undergoing therapy for metastatic castration resistant prostate cancer at the City of Hope Cancer Center

## 14.3 Advertisements

Advertisements to include print, media (radio, television, billboards), telephone scripts, lay summary to be posted on City of Hope's public Clinical Trials On-Line$^{SM}$ website, etc., will be reviewed and approved by the IRB prior to their use to recruit potential study subjects.

## 14.4 Study location and Performance Sites

This study will be performed at City of Hope, City of Hope South Pasadena, and Huntsman Cancer Institute, University of Utah.

## 14.5 Confidentiality

This research will be conducted in compliance with federal and state of California requirements relating to protected health information (PHI). The study will record individual immunological response to the Sipuleucel-T +/- radiation and any side effects, and this will be linked to the subject's identity using a coded study number. The principal investigator, co-investigators, and laboratory technicians will have access to this information, but all information will be treated confidentially. No identifiers will be used in any subsequent publication of these results.}

## 14.6 Financial Obligations and Compensation

Therapy on the protocol utilizes standard of care procedures. The standard of care drug (Sipuleucel-T) and radiation therapy will be the responsibility of the research participant and/or the insurance carrier. The research participant will be responsible for all copayments, deductibles, and other costs of treatment and diagnostic procedures as set forth by the insurance carrier. The research participant and/or the insurance carrier will be billed for the costs of treatment and diagnostic procedures in the same way as if the research participant were not in a research study. However, neither the research participant nor the insurance carrier will be responsible for the research procedures related to this study.

In the event of physical injury to a research participant, resulting from research procedures, appropriate medical treatment will be available at the participating site to the injured research participant, however, financial compensation will not be available. The research participant will not be paid for taking part in this study.

### 14.7 Informed Consent Processes

The Principal Investigator or IRB approved named designate will explain the nature, duration, purpose of the study, potential risks, alternatives and potential benefits, and all other information contained in the informed consent document. In addition, they will review the experimental subject's bill of rights and the HIPAA research authorization form. Research subjects will be informed that they may withdraw from the study at any time and for any reason without prejudice, including as applicable, their current or future care or employment at City of Hope or any relationship they have with City of Hope. Research subjects will be afforded sufficient time to consider whether or not to participate in the research.

Should sufficient doubt be raised regarding the adequacy of comprehension, further clarifications will be made and the questionnaire repeated until a satisfactory result is obtained. Prospective research subjects who cannot adequately comprehend the fundamental aspects of the research study with a reasonable amount of discussion, education and proctoring will be ineligible for enrollment. For those subjects who do comprehend the fundamental aspects of the study, consent will be obtained and documented, followed by eligibility testing. The research team will review the results of eligibility testing and determine if the subject is a candidate for study enrollment.

## 15.0 References

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