CC# 12557: A RANDOMIZED PHASE 2 TRIAL OF IMMEDIATE VS. DELAYED ANTI-CTLA4 BLOCKADE FOLLOWING SIPULEUCEL-T TREATMENT FOR PROSTATE CANCER IMMUNOTHERAPY

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PROTOCOL SYNOPSIS

Study Objectives Phase II Study

Primary

- Determine whether the timing of ipilimumab administration impacts PAP and PA2024-specific immune responses induced by SipT.

Secondary

- Assess the safety associated with giving ipilimumab either immediately following completion of Sipuleucel-T (SipT) or delayed ipilimumab following SipT.
- Assess clinical activity of the combination therapy for each study arm in chemotherapy-naïve patients with metastatic CRPC.
- Determine whether the timing of ipilimumab administration impacts the immunomodulation of activated effector and regulatory T cells.

Study Design

This is a non-comparative open-label randomized multicenter Phase 2 clinical trial combining SipT with ipilimumab in patients with chemotherapy-naïve metastatic CRPC.

All patients will be treated with the fixed treatment backbone of SipT (Q2 wks x 3). Patients will be randomized to one of two arms:

Arm 1 (Immediate Treatment):
Ipilimumab Q3 wks x 4 started 1 day following the final dose of SipT (Day 0).

Arm 2 (Delayed Treatment):
Ipilimumab Q3 wks x 4 started 3 weeks following the final dose of SipT (Day 0).

Following this ipilimumab treatment, patients will then be followed monthly for 3 months and then quarterly until disease progression. The definition of unacceptable toxicity is grade 3 or higher treatment-related toxicities (NCI CTCAE v4) excluding irAEs. The study will assess for the immunogenicity and clinical activity of sequential sipuleucel-T treatment followed by ipilimumab. Patients who experience an initial clinical response to ipilimumab followed by subsequent disease progression will be offered reinduction treatment with ipilimumab.

Sample Size and Population:

Twenty-seven patients will be required in each of the two treatment arms, and up to 54 prostate cancer patients will be required to complete this multicenter study, which includes the initial safety cohort. Men with chemotherapy-naïve metastatic castrate resistant prostate cancer (CRPC) will be candidates for this clinical trial. Other key inclusion criteria include the following:

- Progressive disease after androgen deprivation, as defined by PSA Working Group 2 and/or immune-related response criteria (irRC)
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

- No prior chemotherapy for prostate cancer, with the exception of neoadjuvant chemotherapy
- No prior sipuleucel-T treatment or investigational immunotherapy
- No prostate cancer pain requiring regularly scheduled narcotics.
- No concurrent treatment with systemic steroid therapy

Treatment:

Sipuleucel-T (Provenge) is an FDA-approved autologous cellular immunotherapy designed to stimulate an immune response against prostate cancer. It consists of autologous peripheral blood mononuclear cells (PBMCs), including antigen presenting cells (APCs), which have been activated in vitro with a recombinant fusion protein comprised of prostatic acid phosphatase (PAP) and GM-CSF. Patients will be treated with standard commercial sipuleucel-T (SipT) treatment of 3 planned doses given intravenously (IV) every 2 weeks.

Ipilimumab (Yervoy) is a human anti-CTLA4 monoclonal antibody designed to stimulate immune responses to cancer. It is FDA-approved in the treatment of metastatic melanoma. Patients will receive 4 planned doses of ipilimumab given IV every 3 weeks. Ipilimumab will be given following completion of SipT treatment. Study subjects will be randomized 1:1 to start ipilimumab either 1 day following completion of SipT or 3 weeks following completion of SipT.

Endpoints

Primary

- To assess the impact of the timing of ipilimumab treatment on the induction of IgG antibodies by SipT, the proportion of patients on each study arm who achieve an immune response to PAP and/or PA2024 at study week 20 will be determined. A positive immune response is defined as a titer > 1:400.

Secondary

- To assess the safety of immediate sequential vs. delayed sequential ipilimumab following SipT the maximum grade of each toxicity and adverse event according to the NCI CTCAE v4 as well as immune related adverse events (see section 5.4.5) will be tabulated for each study arm.
- Clinical activity will be assessed separately for each study arm by:
  - the proportion of patients achieving a PSA decline of at least 30% and at least 50% below baseline using PSAWG2 criteria
  - the proportion of patients achieving a radiographic clinical response according to the immune-related response criteria
  - median time to progression with the duration of time to progression for each patient measured from the start of protocol therapy until progression after 4 cycles of protocol therapy
- Modulation of Effector and Regulatory T Cells:
  - Measures of T cell immune activation will be compared between the two study arms. Summary descriptive statistics including means, mean change from baseline and proportions will be presented for each study arm. Measurements of a T cell response to PAP and PA2024 using IFNg ELISPOT will be obtained over time. A positive response

is defined at ≥10 spots/300,000 and will be assessed through week 32. The change from baseline in activated CD4 and CD8 T cells as well as for FoxP3+ CD4+ regulatory T cells will be evaluated through week 20.

PROTOCOL SIGNATURE PAGE

Protocol No.: 12557 **Version Date**: November 17, 2016

1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Committee on Human Research (CHR), and Data Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with applicable CHR requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.
3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
4. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local regulatory requirements. In accordance with the FDA Modernization Act, I will ensure the registration of the trial on the www.clinicaltrials.gov website.
5. I agree to maintain adequate and accurate records in accordance with CHR policies, Federal, state and local laws and regulations.

UCSF Principal Investigator / Study Chair: Lawrence Fong, MD

_____
Printed Name

_____ _____
Signature Date

Participating Site: The University of Texas MD Anderson Cancer Center

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Signature Date

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1 INTRODUCTION

This is a non-comparative open-label randomized phase 2 study to treat patients with chemotherapy-naïve, metastatic CRPC with standard sipuleucel-T (SipT) of 3 treatments Q2 wks. Subjects will then initiate ipilimumab treatment (Q3 wks x 4 doses) either 1 day following the last dose of SipT (immediate arm) or 3 wks following the last dose of SipT (delayed arm) until disease progression or toxicity. Subjects will receive ipilimumab at the 3 mg/kg dose. Twenty-seven evaluable patients will be required per treatment arm, and a total of 54-86 prostate cancer patients will be required to complete this multicenter study. The study will assess immunologic activity of immediate ipilimumab administration following SipT treatment and delayed ipilimumab administration following SipT as measured by immune responses to prostatic acid phosphatase (PAP) and the PAP- GM-CSF fusion protein (PA2024). The latter is the antigen used in producing SipT.

1.1 Research Hypothesis

We hypothesize that combining Sipuleucel T with ipilimumab will enhance the immunogenicity and clinical efficacy as determined by PSA decline and time to progression of this treatment. We also hypothesize that potentiation of PAP-specific T cell responses will be dependent on timing of anti-CTLA-4 administration in relationship to last dose of sipuleucel-T (SipT).

1.2 Background

1.2.1 Sipuleucel –T

1.2.1.1 Pre-Clinical Studies

Pre-clinical studies demonstrated that prostatic acid phosphatase (PAP) can be immunogenic in rats [1]. Antigen presenting cells (APCs) loaded with a fusion protein consisting of rat prostatic acid phosphatase (PAP) coupled to a targeting molecule, rat granulocyte-macrophage colony stimulating factor (GM-CSF), induced strong cellular immune responses in vivo to tissues and tumors that express PAP [2]. Based on these observations, an APC product, designated sipuleucel-T, was developed for the treatment of men with prostate cancer.

1.2.1.2 Clinical Experience of Sipuleucel-T

Sipuleucel-T is an autologous cellular product that is enriched for antigen presenting cells and cocultured ex vivo with a fusion protein comprised of prostatic acid phosphatase (PAP) and GM-CSF (PA2024). While the precise mechanism of how SipT works is not fully elucidated, it is thought to serve as a cellular vaccine against PAP. We initially demonstrated that prostatic acid phosphatase can be immunogenic in rodent models [1]. UCSF has since led phase I, II, and III clinical trials with SipT demonstrating that SipT can induce immune responses and some clinical activity [3,4]. Two randomized, double-blind, placebo-controlled clinical trials have now since demonstrated that SipT enhances overall survival in metastatic, asymptomatic CRPC patients treated with upfront SipT (pre-chemotherapy) [4,5]. In the first randomized, double blind, placebo-controlled, Phase 3 trial (D9901, n = 127 subjects), subjects randomized to sipuleucel-T had a

41% reduction in the risk of death relative to those randomized to placebo (hazard ratio (HR) = 1.71 [95% confidence interval (CI): 1.13, 2.58] $P = 0.010$, 2-sided log rank). 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 with complete follow-up, the survival rate for subjects receiving sipuleucel-T was 34% compared to 11% for subjects receiving placebo ($P = 0.0046$, chi square). In addition, subjects randomized to sipuleucel-T had a 31% reduction in time to disease progression ($P = 0.052$, log rank). The second randomized, double blind, placebo-controlled (IMPACT, n=512 patients) demonstrated a relative reduction of 22% in the risk of death as compared with the placebo group (hazard ratio, 0.78; 95% confidence interval [CI], 0.61 to 0.98; P=0.03) [6]. This reduction represented a 4.1-month improvement in median survival (25.8 months in the sipuleucel-T group vs. 21.7 months in the placebo group). The 36-month survival probability was 31.7% in the sipuleucel-T group versus 23.0% in the placebo group. Despite an overall survival advantage, there was no difference in time to progression (TTP) between the placebo and treatment arms. In patients with advanced disease, generation of an immune response to the vaccine is related to an improved clinical outcome [4](Dendreon, personal communication). Thus increasing the frequency and/or potency of immune responses induced by SipT plus anti-CTLA4 may therefore enhance the clinical efficacy of this treatment.

The overall adverse event (AE) profile observed in the completed Phase 3 studies was similar to the Phase 2 profile. 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, tremor, asthenia, and vomiting. These events were generally mild or moderate in severity and resolved within 1 to 2 days.

A possible increased risk of cerebrovascular events has been observed. For all randomized studies conducted to date, the incidence of cerebrovascular events of any etiology was 3.9% in subjects treated with sipuleucel-T (18 of 461 subjects) compared with 2.6% in subjects treated with placebo (6 of 231 subjects). The odds ratio (OR) for risk of stroke in the sipuleucel-T arm relative to the control arm is 1.52, with the 95% CI overlapping 1.00 (95% CI: 0.60, 3.89]; $P = 0.510$). The incidence of hemorrhagic events was 0.7% in subjects treated with sipuleucel-T compared to 0.4% in subjects treated with placebo; the incidence of ischemic events was 2.4% compared to 2.2%, respectively; and 4 cerebrovascular events in subjects treated with sipuleucel-T were of unknown etiology (0.9%). The majority of cerebrovascular events were not fatal, with 1.5% and 0.9% of the events resulting in death for subjects treated with sipuleucel-T and placebo, respectively (OR = 1.76 [95% CI: 0.36, 8.57]; $P = 0.725$). Conclusions regarding the increased risk of cerebrovascular events cannot be drawn at this time given the small number of events and large confidence intervals. Additional studies are underway to better characterize these events.

1.2.2 Ipilimumab

1.2.2.1 Pharmacology of Ipilimumab

Ipilimumab is a human immunoglobulin G (IgG1)κ anti-CTLA-4 monoclonal antibody (mAb). In vitro studies were performed with ipilimumab to demonstrate that it is specific for CTLA-4, actively inhibits CTLA-4 interactions with B7.1 and B7.2, does not show any cross-reactivity with human B7.1, B7.2 negative cell lines, and stains the appropriate cells without non-specific

cross-reactivity in normal human tissues, as demonstrated by immunohistochemistry. Ipilimumab does cross-react with CTLA-4 in non-human primates including cynomolgus monkeys.

Ipilimumab was originally produced and purified from a hybridoma clone. Subsequently, a transfectoma (CHO cell) has been generated that is capable of producing more ipilimumab on a per cell basis than the hybridoma. Material from the transfectoma will be utilized in this and future ipilimumab clinical studies. Biochemical, immunologic and in vivo preclinical primate assessments demonstrated similarity between hybridoma and transfectoma-derived ipilimumab.

1.2.2.2 Pre-Clinical Toxicology of Ipilimumab

Complete information on the pre-clinical toxicology studies can be found in the Ipilimumab Investigator Brochure (IB). Non-clinical toxicity assessments included in vitro evaluation for the potential of ipilimumab to mediate complement-dependent cellular cytotoxicity (CDCC) or antibody-dependent cellular cytotoxicity (ADCC), and toxicology assessments in cynomolgus monkeys alone and in the presence of vaccines.

The in vitro studies demonstrated that ipilimumab did not mediate CDCC of PHA- or CD3-activated human T cells. However, low to moderate ADCC activity was noted at concentrations up to 50 ug/mL. These data are consistent with the requirement of high levels of antigen expression on the surface of target cells for efficient ADCC or CDCC. Since ipilimumab is a human IgG1, an isotype generally capable of mediating CDCC and ADCC, the lack of these activities is likely due to a very low expression of CTLA-4 on activated T cells. Therefore, these data suggest that ipilimumab treatment would not result in depletion of activated T cells in- vivo. Indeed, no depletion of T cells or T cell subsets were noted in toxicology studies in cynomolgus monkeys.

No mortality or signs of toxicity were observed in three independent 14-day intravenous toxicology studies in cynomolgus monkeys at multiple doses up to 30 mg/kg/dose. Furthermore, ipilimumab was evaluated in sub chronic and chronic toxicology studies in cynomolgus monkeys with and without Hepatitis B (HepB) Vaccine and Melanoma Vaccine. Ipilimumab was well tolerated alone or in combination in all studies. There were no significant changes in clinical signs, body weight values, clinical pathology values or T cell activation markers. In addition, there were no significant histopathology changes in the stomach or colon.

1.2.2.3 Human Pharmacokinetics of Ipilimumab

Pharmacokinetic (PK) profiles for ipilimumab have been analyzed. The primary objective of Protocol MDX010-015 was to determine the safety and PK profile of single and multiple doses of ipilimumab derived from a transfectoma or hybridoma cell line. Mean plasma concentrations of ipilimumab administered at doses of 3 mg/kg (hybridoma-derived drug product); 2.8 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, and 20 mg/kg (transfectoma-derived drug product) demonstrated approximate dose proportionality. Equimolar doses of hybridoma-derived and transfectoma-derived drug product had comparable PK profiles. The range of mean volume of distribution at steady state (Vss) across cohorts 2.8, 3, 5, 7.5, 10, 15, and 20 mg/kg, was 57.3 to 82.6 mL/kg, indicating drug distribution was mostly limited to the intravascular space. The clearance was low (range 0.11 to 0.29 mL/h/kg) and reflective of the half-life (range 297 to 414 h), which is consistent with the long terminal disposition phase of ipilimumab. There was

moderate variability in the PK parameters among subjects, with CV of 11% to 48% in AUC (0-21d), 20% to 59% in CL, and 17% to 46% in Vss.

1.2.2.4 Clinical Experience with Ipilimumab

Ipilimumab is has been shown to improve overall survival in patients with advanced melanoma (unresectable Stage III or Stage IV) [7,8]. These results prompted FDA-approval of ipilimumab for the treatment of advanced melanoma in 2011.

Ipilimumab has been administered to approximately 2901 patients with different cancers in 25 completed or ongoing clinical trials as of 31-Mar-2009 with a dose range between 0.3 mg/kg and 20 mg/kg and in various combinations.

In general, the safety profile of ipilimumab administered as single doses of up to 20-mg/kg and multiple doses of up to 10 mg/kg every 3 weeks was characterized by adverse reactions that were mostly immune in nature. Drug-related SAEs were reported in studies of ipilimumab administered as monotherapy, as well as in combination with vaccines, cytokines, chemotherapy, or radiation therapy.

The overall summary of safety for the 2901 patients treated with ipilimumab in the completed or ongoing clinical trials and the subset of 658 patients treated at the 10 mg/kg dose level is presented in Table 1.

Table 1: Ipilimumab – Overall Summary of Safety

	Number of Subjects (%)	
	Ipilimumab 0.3 – 20 mg/kg N = 2901	**Ipilimumab 10 mg/kg N = 658**
Any Drug-related AE	2357 (81.2)	561 (85.3)
Grade 1	699 (24.1)	158 (24.0)
Grade 2	889 (30.6)	198 (30.1)
Grade 3	617 (21.3)	163 (24.8)
Grade 4	127 (4.4)	38 (5.8)
Grade 5	20 (0.7)	4 (0.6)
Any Serious Adverse Events	1258 (43.4)	310 (47.1)
Grade 3 – 4	806 (27.8)	179 (27.2)
Any Drug-related Serious Adverse Events	595 (20.5)	179 (27.2)
Grade 3 – 4	469 (16.2)	140 (21.3)

1.2.2.5 Details of Drug-Related Adverse Events

Treatment-emergent adverse events (AEs) considered by the investigator to be related to study drug were reported for 81.2% of all treated subjects and 85.3% of subjects treated with ipilimumab at 10 mg/kg.

Among all treated subjects, the most frequently reported treatment-related AEs of any grade included fatigue (27.8%), diarrhea (27.5%), nausea (23.4%), rash (21.8%), pruritus (19.9%), pyrexia (11.9%), and vomiting (11.7%).

Similarly, among subjects treated with ipilimumab at 10 mg/kg, the most frequently reported treatment-related AEs of any grade included diarrhea (38.1%), fatigue (30.5%), rash (34.5%), pruritus (29.8%), nausea (17.6%), pyrexia (12.3%), vomiting (10.9%) and colitis (10.2%).

1.2.2.6 Immune-Related Adverse Events (irAEs) with Ipilimumab

Many of the adverse events considered related to ipilimumab may be immune in nature and presumably a consequence of the intrinsic biological activity of ipilimumab. An irAE is defined as any adverse event associated with drug exposure and consistent with an immune-mediated event. Disease progression, infections and other etiologic causes are ruled out or deemed unlikely as contributing to the event. Supportive data, such as autoimmune serology tests or biopsies, are helpful but not necessary to deem an event an irAE. Events of unclear etiology, which were plausibly "immune-mediated" have been conservatively categorized as irAEs even if serologic or histopathology data are absent. These irAEs likely reflect a loss of tolerance to some self-antigens or an unchecked immune response to gut or skin flora. Some breakthrough of immunity may be inseparably linked to the clinical antitumor activity of ipilimumab.

Immune-related AEs predominately involve the GI tract, endocrine glands, liver or skin.

Among all 2901 treated subjects, 59.6% (1729/2901) of subjects reported any irAE and 15.2% (441/2901) of subjects reported serious irAEs. Among subjects who received ipilimumab at 10 mg/kg, 21.9% (144/658) of subjects reported serious irAEs.

Table 2 summarizes the incidence of serious irAEs among all treated subjects and subjects who received ipilimumab 10 mg/kg.

Table 2: Serious Immune-related Adverse Events Reported for at Least 2% of Subjects in any Event Category

	Number of Subjects (%)	
	Ipilimumab 0.3 – 20 mg/kg N = 2901	**Ipilimumab 10 mg/kg N = 658**
irAEs[a]		
Any	441 (15.2)	144 (21.9)
Grade 3	298 (10.3)	87 (13.2)
Grade 4	59 (2.0)	25 (3.8)
GI irAE[a]		
Any	236 (8.1)	85 (12.9)
Grade 3	166 (5.7)	58 (8.8)
Grade 4	17 (0.6)	10 (1.5)
Liver irAE[a]		
Any	109 (3.8)	33 (5.0)

Table 2: Serious Immune-related Adverse Events Reported for at Least 2% of Subjects in any Event Category

	Number of Subjects (%)	
Grade 3	72 (2.5)	18 (2.7)
Grade 4	32 (1.1)	13 (2.0)
Endocrine irAE[a]		
Any	61 (2.1)	21 (3.2)
Grade 3	44 (1.5)	12 (1.8)
Grade 4	3 (0.1)	1 (0.2)

[a]Based on treatment-related adverse events retrieved from the clinical database using pre-defined MedDRA terms that were considered potential irAEs.

With few exceptions, irAEs were clinically manageable and reversible with supportive care or corticosteroids. Management algorithms are included in the IB.

Corticosteroid treatment did not adversely affect antitumor responses in those subjects who had both an irAE requiring steroid therapy and an objective tumor response. Systemic corticosteroids do not appear adversely associated with ipilimumab-induced clinical response when used to manage irAEs in patients with advanced melanoma. Similar results were observed regardless of whether mWHO or the novel immune-related response criteria (irRC) [9] were used. Steroids can be used promptly to manage severe irAEs and minimize the risk for serious complications[10].

In the setting where subjects were enrolled to receive ipilimumab every 3 weeks dosing until progression, irAEs could be reported at any time, with colitis and rash reported most often during the early doses and hypophysitis reported with later doses.

Gastrointestinal irAEs

The most common Grade 3 or greater irAE involved the lower GI tract and clinically manifested as diarrhea or hematochezia. Diarrhea resulting from treatment with ipilimumab ranged from mild to severe and was life-threatening in some cases. Some cases of diarrhea began as mild and became very severe. Among subjects who received ipilimumab at 10 mg/kg, GI irAEs of any grade were reported for 40.0% (263/658) of subjects, and Grade 3 – 4 GI irAEs were reported for 12.6% (83/658) of subjects. Serious GI irAEs, mostly involving diarrhea or colitis, were reported in 12.9% (85/658) of subjects treated with ipilimumab at 10 mg/kg.

Inflammatory Hepatotoxicity

Immune-related hepatic dysfunction, including hepatitis or abnormal liver function tests (LFT) attributed to ipilimumab therapy, has been reported. Subjects may develop elevations in LFTs in the absence of clinical symptoms. Inflammatory hepatotoxicity includes non-infectious hepatitis (e.g., autoimmune hepatitis). Among subjects who received ipilimumab at 10 mg/kg, inflammatory hepatotoxicity of any grade was reported for 9.0% (59/658) of subjects, and Grade 3 – 4 inflammatory hepatotoxicity was reported for 6.4% (42/658). Serious inflammatory hepatotoxicity has been reported in 5.0% (33/658) of subjects who received ipilimumab at 10 mg/kg. Inflammatory hepatotoxicity is usually reversible when immediately treated with high-dose steroids, if applicable, with or without additional immunosuppressants as recommended in the hepatotoxicity management algorithm presented as an appendix in the IB.

Hypophysitis/Hypopituitarism and Other Endocrine Conditions

Hypophysitis/hypopituitarism, clinically manifested by fatigue, has been reported. Most subjects with hypopituitarism presented with nonspecific complaints such as fatigue, confusion, visual disturbance, or impotence. Some had headache as the predominant presentation. The majority of subjects with hypopituitarism demonstrated enlarged pituitary glands based on brain magnetic resonance imaging (MRI). Low adrenocorticotropic hormone (ACTH) and cortisol were the most common biochemical abnormality reported; low thyroid stimulating hormone (TSH), testosterone, or prolactin was also reported in some subjects[11].

Hypophysitis/hypopituitarism was controlled with appropriate hormone-replacement therapy and may be dose related. Among subjects who received ipilimumab at 10 mg/kg, endocrinopathy of any grade was reported for 7.6% (50/658) of subjects, and Grade 3-4 endocrinopathy was reported for 2.4% (16/658) of subjects. Serious drug-related endocrinopathy, such as hypophysitis/hypopituitarism, was reported in 3.2% (21/658) of subjects who received ipilimumab at 10 mg/kg.

The first onset of endocrine irAEs typically occurred between weeks 6 and 12 of treatment. Endocrine events were generally manageable with hormone-replacement therapy, and the majority of subjects were not weaned from steroids.

Rash and Other Skin Conditions

Rash was one of the most common irAEs, and most cases were Grade 1 or 2 in intensity; pruritus has also been reported[12]. When biopsied, pleomorphic infiltrates were noted in the skin. Among subject who received ipilimumab at 10 mg/kg, skin irAEs of any grade were reported for 52.9% (348/658) of subjects, and Grade 3 – 4 skin irAEs were reported for 2.9% (19/658) of subjects. Serious skin irAEs were reported in < 1% (4/658) of subjects who received ipilimumab at 10 mg/kg. Skin irAEs were generally reversible.

Other presumed irAEs reported include, but were not limited to, arthritis/arthralgias, pneumonitis, pancreatitis, autoimmune (aseptic) meningitis, autoimmune nephritis, pure red cell aplasia, non-infective myocarditis, ocular inflammation, Guillain-Barre syndrome (GBS), myasthenia gravis, and neuropathy (e.g., motor neuropathy, neuritis), of which were individually reported for < 1% of subjects.

Other reported irAEs

Ocular inflammation, manifested as Grade 2 or Grade 3 episcleritis or uveitis, was associated with concomitant diarrhea in a few subjects and occasionally occurred in the absence of clinically apparent GI symptoms[13]. Serious ocular inflammation was reported in 1 of 658 (0.2%) subjects who received ipilimumab at 10 mg/kg (8 [0.3%] of 2901 subjects program-wide reported serious ocular inflammation). Preliminary analysis (based on the manual extraction of the SAE data from the internal safety database) indicated that the median time to event onset was approximately 61 days (range: 14 – 114 days). Based on the available data with known outcome, most of the subjects recovered or improved with or without corticosteroid therapy with a median duration of approximately 6 days (range: 5 – 23 days).

Management algorithms for general irAEs, and ipilimumab-related diarrhea, hepatotoxicity, endocrinopathy, and neuropathy are presented as appendices in this protocol.

Additionally, as of February 2006, there has been observation from a National Cancer Institute (NCI) study of bowel wall perforation in some patients who were administered a high-dose IL-2

following treatment with ipilimumab. Of the 22 patients administered high-dose IL-2, three patients experienced bowel wall perforations. This is a higher rate than would be expected with high-dose IL-2 treatment alone. All three patients had metastatic melanoma and had previously received their last dose of ipilimumab > 77 days before the first dose of IL-2. Two of the patients had clinically significant ipilimumab-related diarrhea or colitis and the symptoms had completely resolved prior to IL-2 administration. One patient did not experience ipilimumab-related diarrhea. It is unknown whether this observation represents a true association or is mechanistically unrelated to prior ipilimumab exposure.

1.2.2.7 Drug-Related Deaths

Based on reports from the safety database as of June 30, 2009, there have been reports of death (approximately 1% [35/3800]), deemed by the investigator as possibly related to the administration of study drug. The most common cause of drug related deaths was GI perforation. Other causes included multiorgan failure, sepsis, hypotension, acidosis, and adult respiratory distress syndrome. For details on all drug-related deaths, refer to the current version of the Ipilimumab Investigator Brochure.

1.2.2.8 Safety of 10 mg/kg Multiple Doses

Based on a review of the program-wide SAE data as previously reported, evidence had suggested that ipilimumab-associated irAEs were dose dependent in frequency, and higher irAE rates had been observed at 10 mg/kg than at lower doses of ipilimumab. Subsequently, this dose-dependent effect was further demonstrated in CA184-022 in which three dose levels of ipilimumab were studied, including 0.3 vs. 3 vs. 10 mg/kg. Table 3 summarizes the overall irAE frequencies by dose from CA184-022 based on safety data from the locked clinical database.

Table 3. Summary of Immune-Related Adverse Events (irAEs) by Treatment Groups – Treated Subjects (CA184-022)

	Number of Subjects (%)		
	Ipilimumab		
	0.3 mg/kg (N=72)	3 mg/kg (N=71)	10 mg/kg (N=71)
Overall irAEs	26.4	64.8	70.4
Grade 3-4	0	7.0	25.4
GI irAEs	16.7	32.4	39.4
Grade 3-4	0	2.8	15.5
Hepatic irAEs	0	0	2.8
Grade 3-4	0	0	2.8
Endocrine irAEs	0	5.6	4.2
Grade 3-4	0	2.8	1.4
Skin irAEs	12.5	45.1	46.5
Grade 3-4	0	1.4	4.2

1.2.2.9 Neuropathies

Isolated cases of motor neuropathy of an autoimmune origin have been reported among patients treated with ipilimumab. Three cases have been diagnosed as Guillain-Barre syndrome (GBS), two of which were considered study related. In both cases, the GBS was atypical in nature and more clinically resembled polyneuritis. As of 30 June 2009, 27 cases of neuropathy SAEs have been reported. Of these, 22 were assessed as unrelated to study therapy because alternative etiologies, including brain metastases, spinal cord compression, arterial thrombosis, or platinum-base chemotherapy were identified in almost every case.

1.2.3 Clinical Efficacy of Ipilimumab

Treatment with ipilimumab has demonstrated clinically important and durable tumor responses in several malignancies including melanoma, prostate cancer, and renal cell carcinoma. The most extensively studied tumor type has been malignant melanoma and the principal demonstration of the efficacy of ipilimumab at the 10 mg/kg dose comes from 3 Phase 2 multicenter trials in 487 subjects with advanced melanoma: CA184022, CA184008, and CA184007[14].

The overall survival (OS) results from these 3 completed primary Phase 2 studies are presented in Table 4

Table 4 Updated Overall Survival Results for 3 Primary Studies in Advanced Melanoma (as of 09-Mar-2009)

	CA184022	CA184008	CA184007	
	All Randomized	All Treated	All Randomized[a]	
Parameter	Ipilimumab 10 mg/kg N = 72	Ipilimumab 10 mg/kg N = 155	Ipilimumab 10 mg/kg + Placebo N = 57	Ipilimumab 10 mg/kg + Budesonide N = 58
OS, Median (Months) 95% CI (Months)[b]	11.43 (6.90, 16.10)	10.22 (7.59, 16.30)	19.29 (11.99, --)	17.68 (6.80, --)
Survival Rate at 1 Year (%) 95% CI (%)[c]	48.64 (36.84, 60.36)	47.22 (39.52, 55.11)	62.41 (49.37, 75.07)	55.87 (42.71, 68.79)
Survival Rate at 2 Years (%) 95% CI (%)[c]	29.81 (19.13. 41.14)	32.83 (25.37, 40.49)	41.78 (28.30, 55.46)	40.57 (27.12, 54.37)

[a] Data are presented for the per-protocol mixed population of pretreated and previously untreated subjects.

[b] Based on Kaplan-Meier estimation and CI computed using the bootstrap method.

[c] Median and associated 2-sided 95% CIs calculated using the method of Brookmeyer and Crowley.

Further details on clinical results can be found in the current version of the Ipilimumab Investigator Brochure.

1.2.4 Ipilimumab in Prostate Cancer Patients

Although Ipilimumab is a fully human anti-CTLA-4 IgG_1 monoclonal antibody approved in the US for the treatment of unresectable advanced melanoma, it was in fact first administered to patients with prostate cancer. In this initial trial, a single dose of ipilimumab at 3mg/kg given to patients with hormone-refractory prostate cancer resulted in a ≥ 50% decline in PSA levels in 2 of 14 patients, and <50% decline in 8 others [15]. The two responders did not have measureable disease, but one developed grade 3 toxicity of an inflammatory nature (rash). Of the two other patients who had measureable disease at baseline that were evaluated by repeat radiographic imaging, neither demonstrated an objective response using the Response Evaluation Criteria in Solid Tumors (RECIST). This trial showed that a single 3mg/kg dose of ipilimumab is tolerated but also indicated the risk of treatment-related immune events.

Overall, there have been ten clinical trials that are exploring the use of anti-CTLA-4 antibodies in the setting of prostate cancer. As a result of the data from TRAMP mice that were treated with anti-CTLA-4 antibodies combined with other treatments, six clinical trials have explored combinations with other immune adjuvants (GM-CSF), cancer vaccines (GVAX and PROSTVAC), chemotherapy, radiation and anti-androgen therapy. Although the studies are too small to be definitive, these trials overall have noted declines in PSA and a low frequency of radiographic responses at doses of ipilimumab ≥ 3mg/kg. Radiographic responses in prostate cancer can be difficult to detect because bone metastasis, which are common with prostate cancer, are difficult to measure. In a Phase I trial combining GM-CSF with escalating doses of ipilimumab, 22% of patients receiving ipilimumab ≥ 3mg/kg experienced a significant PSA response [16,17]. At the time of this report, 1 patient had a partial objective response in liver metastases in accordance with RECIST. Combining cancer vaccines and ipilimumab would presumably improve anti-tumour activity by amplifying immune responses focused to relevant antigens as demonstrated in mice. In a trial investigating ipilimumab with GVAX, 5 of 28 patients who completed treatment had a ≥ 50% decline in PSA, and 12 had stabilization of metastatic bone disease for extended durations (12 to 21 months) [18,19,20]. PROSTVAC has also been combined with ipilimumab. In a randomized phase II trial, PROSTVAC alone significantly improved overall survival over placebo in healthy, well-performing patients with mAIPC [21]. In the combination trial, 5 of 9 chemo-naïve patients with mAIPC who received 3 or 5 mg/kg of ipilimumab plus PROSTVAC had ≥ 50% declines in PSA [22]. Overall 14 of 30 patients at any dose level of ipilimumab (1, 3, 5 and 10 mg/kg) had some decline in PSA. Physical tumor shrinkage however was infrequent. Of the previous 9 patients, 4 had stable disease ≥ 6 months, and 2 had unconfirmed partial responses. Nine of 15 receiving 10 mg/kg of ipilimumab had stable disease ≥ 6 months. Despite limited numbers of noticeable tumor shrinkage, both GVAX and PROSTVAC with ipilimumab trials showed a significant number of patients with stabilization of their disease under combination therapy that can last for several months and manageable side effects. However, further studies are required to see if the combination is more effective than either ipilimumab or vaccine alone.

In a phase II trial that combined ipilimumab with radiotherapy, no difference in the number of patients who had a decline in PSA ≥ 50% was seen between patients treated with ipilimumab alone (5 out of 16 chemo-naïve patients) versus the ipilimumab and radiotherapy(4 out of 15 chemo-naïve patients), and fewer patients in the post-chemotherapy group had a decline in PSA ≥ 50% when treated with ipilimumab and radiation (1 out of 14) [23,24]. In a randomized phase II

trial comparing ipilimumab at 3mg/kg alone versus ipilimumab plus a single dose of docetaxel showed a limited number of PSA responses: 2 of 23 patients treated with ipilimumab alone and 1 of 20 patients treated with the combination therapy[25]. There was no objective radiographic response observed at the time. However, in a randomized phase II trial of ipilimumab and androgen ablation, patients treated with ipilimumab and androgen ablation were more likely to have undetectable levels of PSA by 3 months (55% vs. 38%) [26]. Another human IgG_2 monoclonal antibody (tremelimumab, Pfizer) has been tested in a phase I trial in combination with androgen deprivation in patients with PSA-recurrent non-metastatic prostate cancer but the results are not currently available at the time of writing (www.ClinicalTrials.gov, Identifier: NCT00702923) [27].

Blocking CTLA-4 in patients with prostate cancer revealed tumour response patterns not previously appreciated in inbred mouse models. For example, a decline in PSA levels can occur immediately after treatment but also after a period of stable disease or even after disease progression. For early phase trials, which are designed to capture early endpoints, such as safety or PSA responses, not enough time may have elapsed to see objective tumour responses by RECIST. Even so, more patients achieve disease stabilization rather than tumour shrinkage by radiographic assessment. One potential explanation is that AIPC mostly metastasizes to the bone, and bone lesions, whether regressing or progressing, are notoriously difficult to measure with current radiographic techniques. On the other hand, these response patterns have been consistently observed in patients with measureable metastases in advanced melanoma[28], yet objective responses still remain low overall (~10%) [29]. If tumour control is sustained, however, patients may live longer. Indeed, the median overall survival in the PROSTVAC combination trial is 31.8 months [30], a significant duration in mAIPC, and in pre-treated metastatic melanoma, CTLA-4 blockade significantly improves survival by 4 months over gp100 vaccine, despite no improvement in time to progression or progression-free survival [7].

1.2.4.1 Rationale for 3 mg/kg Dose of Ipilimumab

Given this experience with CTLA-4 blockade in AIPC, two recent phase III trials have investigated ipilimumab in mAIPC with overall survival as the primary endpoint. The first study compared ipilimumab versus placebo in individuals with mAIPC who have not already been treated with chemotherapy. The second trial compared ipilimumab following radiation therapy versus placebo following radiation therapy in patients who have already been treated with docetaxel chemotherapy for mAIPC.[47] Both studies addressed as their primary endpoint whether patients live longer with CTLA-4 blockade than patients treated in the control arm.

While the second study in metastatic prostate cancer did not meet the primary endpoint of improving overall survival (HR=0.85, p=0.053), Ipilimumab demonstrated antitumor activity in other efficacy endpoints, including progression-free survival. More importantly, safety was evaluated for all treated patients (pts; N=393 for ipilimumab 10 mg/kg, N=396 for placebo) starting from first study dose and ending 70 days after the last study dose, including maintenance dosing. Any grade (Gr) irAEs occurred in 63.4% and 21.7% of patients in the ipililimumab and placebo arms, respectively. Most common Gr 3/4 irAEs were gastrointestinal (GI) (18.1%; mostly diarrhea and colitis). Deaths due to study drug toxicity, as per investigators, occurred in 4 patients (4, ipilimumab and 0, placebo).

Thus, based on the above safety data from the second phase III trial which showed severe irAEs, the most frequent being diarrhea and colitis, the dose of ipilimumab has been reduced from 10 mg/kg to 3 mg/kg.

1.3 Study Rationale

Multiple animal models have demonstrated additive or synergistic immunologic and anti-tumor effects in combining CTLA4 blockade with a vaccine [31-34]. While these results provide a compelling rationale for pursuing a combination trial, a randomized trial to demonstrate a clinical advantage to combining CTLA4 blockade with SipT would require overall survival as the evaluable endpoint (because the clinical efficacy of SipT can only be demonstrated by overall survival, not TTP or response rate). Two crucial issues must be addressed prior to pursuing such a trial: 1) safety of sequential treatment, and 2) timing of the ipilimumab administration.

While the importance of demonstrating safety is obvious, the importance of timing is also crucial: in the proHA x TRAMP mouse model, initiation of CTLA4 blockade 1 day following vaccination was superior to initiation of CTLA4 blockade 4 days following vaccination in inducing T cell immune responses (Dr. Chuck Drake, Johns Hopkins, manuscript in progress, personal communication). With regards to SipT, the cellular product is known to also contain lymphocytes. While characterization of this product is limited at present, CD54 upregulation represents one of the key release criteria for this cellular product. While CD54 represents an activation marker on antigen presenting cells, it can also be an activation marker for lymphocytes. We now know that in fact lymphocytes do also significantly upregulate CD54, particularly in the second and third doses of SipT. This finding would suggest that activated T cells, which would express higher levels of CTLA4, may be contained in the product. Therefore, these later cellular products may in fact represent antigen specific lymphocytes that have been primed in vivo (with the first dose) and expanded with the ex vivo culture (2nd and 3rd doses). If this is true, then CTLA4 blockade would be most effective at potentiating these T cells when given soon after the final SipT infusion. Otherwise, if significant time elapses between infusion of SipT and CTLA4 blockade, then those activated (CTLA4-expressing) T cells induced in/by the product may already have encountered endogenous costimulatory molecules, and may thus have already triggered CTLA4-mediated down-modulation of their function. Alternatively, immediate administration of ipilimumab with activated T cells may potentially increase the frequency of toxicities or the generation of adaptive regulatory T cells.

Our trial design of studying sequential treatment with ipilimumab following SipT represents the schedule that is currently clinically feasible. No data are available as to whether the presence of ipilimumab within a patient may alter the SipT product. Because the sipT product has specific release criteria, SipT treatment will be completed prior to treatment with ipilimumab in order to not jeopardize the production the SipT.

PSA decline of > 50% was chosen as a secondary endpoint of this study given the difficulty of evaluating prostate cancer patients radiographically. Metastatic disease is primarily unmeasurable and bone scans rarely show the improvement that would reflect response and clinical benefit. To include only patients with measurable disease would limit the applicability of this therapy to a very limited subset of patients. Although PSA decline is not a widely accepted surrogate endpoint, it is often used as the primary endpoint in clinical studies.

Results from efficacy studies of ipilimumab in advanced melanoma have shown both the 3 and 10 mg/kg ipilimumab doses are safe and effective. Ipilimumab was approved in US and Europe at a dose of 3 mg/kg in adults patients with advanced melanoma based on a phase 3 study in patients with previously treated melanoma (MDX010-20). Ipilimumab 10 mg/kg was used in a second registrational study in adult patients with previously untreated advanced melanoma and prolonged overall survival when combined with DTIC, versus DTIC alone (CA184-024). A randomized phase 2 study in advanced melanoma (CA184-022) suggested that10 mg/kg ipilimumab was potentially more active and was associated with increased toxicities relative to 3 mg/kg dose. An ongoing phase 3 trial (CA184169) of 3 vs. 10 mg/kg ipilimumab will provide definitive answer regarding whether there is an optimal monotherapy dose in advanced melanoma.

The dosing interval for ipilimumab is based on the prior study which demonstrated drug levels ≥ 10 mg/mL (a minimum level required for CTLA-4 blockade in pre-clinical models) for greater than 28 days. Four doses of ipilimumab given every 3 weeks were chosen because four doses have been given safely in other trials.

2 STUDY OBJECTIVES: PHASE II STUDY

2.1 Primary Objective

- Determine whether the timing of ipilimumab administration impacts PAP and PA2024-specific immune responses induced by SipT.

2.2 Secondary Objectives

- Assess the safety associated with giving ipilimumab either immediately following completion of SipT or delayed ipilimumab following SipT.
- Assess clinical activity of the combination therapy for each study arm in chemotherapy-naïve patients with metastatic CRPC.
- Determine whether the timing of ipilimumab administration impacts the immunomodulation of activated effector and regulatory T cells.

3 STUDY DESIGN

This is a non-comparative open-label randomized multicenter Phase 2 clinical trial administering ipilimumab following standard SipT treatment in patients with chemotherapy-naïve metastatic CRPC. Patients will be accrued at UCSF and MD Anderson. Patients are randomized so as to achieve uniform patient cohorts treated on each regimen. Twenty-seven evaluable patients will be required per treatment arm, and 54-66 prostate cancer patients will be required to complete this multicenter study. The study will assess for the immunogenicity and clinical activity of sipuleucel-T treatment followed by ipilimumab in chemotherapy-naïve patients with metastatic castrate resistant prostate cancer (CRPC).

All patients will be treated with standard SipT (Q2 wks x 3). Patients will be randomized within 2 weeks of their final dose of SipT to one of two arms:

Arm 1 (Immediate Treatment)

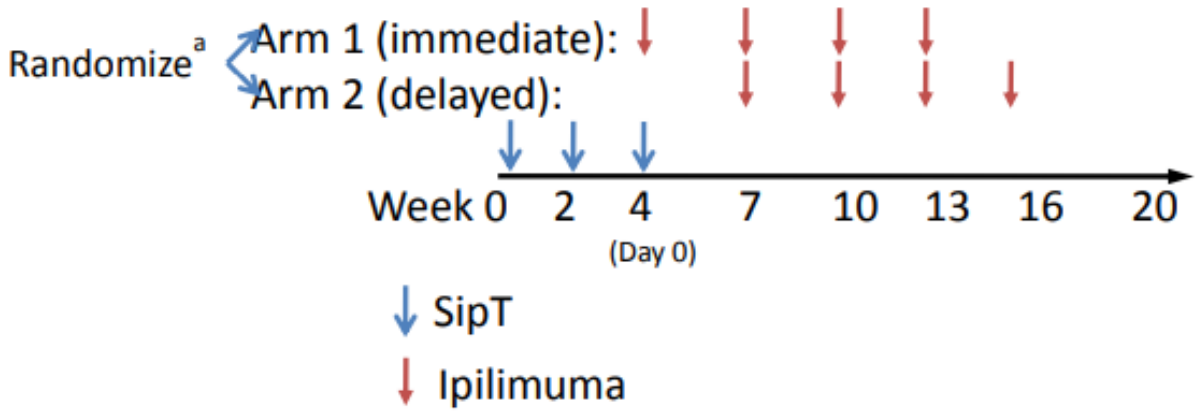
Ipilimumab Q3 wks x 4 started 1 day following the final dose of SipT.

Arm 2 (Delayed Treatment)

Ipilimumab Q3 wks x 4 started 3 weeks following the final dose of SipT.

Following this "induction" ipilimumab treatment, patients will then be followed monthly for 3 months and then quarterly (every 12 weeks) until disease progression. The definition of unacceptable toxicity is grade 3 or higher treatment-related toxicities (NCI CTCAE v4) excluding irAEs. Patients who experience an initial clinical responses to ipilimumab followed by subsequent disease progression will be offered reinduction treatment with ipilimumab.

Figure 1. Dosing Schema



[a]Randomizaiton will be stratified by site and will occur within 2 weeks prior to the final Sip T dose.

3.1 Safety Analysis

Because SipT treatment is associated with minimal toxicity, and an active dose of ipilimumab has been established (no MTD has been defined) with tolerable side effects, we propose to perform a safety analysis with standard SipT treatment and the 3 mg/kg dose of ipilimumab. Twelve patients will be randomized to either of the 2 scheduling arms (immediate vs. delayed) (6 per arm). After randomizing the initial 6 patients to each arm, the frequency and grade of AEs will be evaluated.

3.2 Phase 2 Design

Once the ipilimumab dose is established for each study arm, the randomization between the immediate and delayed arms will resume accruing a total of 27 evaluable randomized patients per study arm.

Randomized patients treated in the phase I at the same dose used in the Phase 2 study will be included for immune response analysis; thus patients accrued in the randomized component of the Phase I trial can be included for analysis of the study objectives.

Once written informed consent is obtained and the patient has undergone screening and determined to be eligible for the trial, treatment with SipT will begin. The patient will be randomly assigned following the second dose of SipT to one of the two treatment groups in a 1:1 ratio using a block design to maintain a balance in treatment assignment. Randomization will be stratified by site (UCSF and MD Anderson). The randomization will be performed by the study statistician at UCSF. At the time of randomization, a unique patient study identification number will be assigned to each patient. This study identification number must be included on all submitted forms and specimens.

Patients will receive induction treatment with 4 doses of ipilimumab on a 21-day cycle. As durable disease stabilization and/or objective tumor response can be seen after early progression, it is recommended that, in the absence of dose-limiting toxicities, all four doses of ipilimumab be administered over the initial 12 weeks even in the setting of apparent clinical progression, providing the subject's performance status remains stable.

All subjects who enter the induction period, including those who may have discontinued treatment for drug-related AEs and/or who have evidence of clinical progression during the induction period, should obtain a 12-week tumor assessment.

Clinical progression warranting alternative anti-cancer treatment should be considered only in subjects whose overall tumor burden appears to be substantially increased and/or in subjects whose performance status is decreased.

3.3 Reinduction Treatment

Patients who experience a clinical response to treatment during the first 12 weeks of ipilimumab treatment, but then develop subsequent progression of their disease after the initial 12 weeks of ipilimumab and who have not experienced unacceptable toxicity (refractory Grade > 3 irAEs) can be offered reinduction therapy with ipilimumab with up to 4 doses Q3 wks at the same dose level.

Following discontinuation of study therapy, subjects will complete a 30-day off study visit and then enter into follow up. Subjects who discontinue ipilimumab treatments should be followed until death or closure of the study (whichever is first). Subjects who are no longer receiving ipilimumab because of clinical progression and who have switched to alternative treatment are not followed formally except to record the date of death.

4 SUBJECT SELECTION CRITERIA

For entry into the study, the following criteria MUST be met. Any exceptions from the protocol-specific selection criteria must be approved by the Principal Investigator and/or the Institutional Review Board (IRB) before enrollment.

4.1 Inclusion Criteria

1) Histologically confirmed, metastatic prostate adenocarcinoma (positive bone scan and/or measurable disease on CT scan and/or MRI of the abdomen and pelvis).
2) History of progressive disease after androgen deprivation, defined by one OR both of the following:

- Objective radiographic progression defined by PCWG2[39] or RECIST criteria[40]
- PSA evidence for progressive prostate cancer which consists of a PSA level of at least 2 ng/ml, which has risen on at least 2 successive occasions, at least 1 week apart. If the confirmatory PSA (#3) value is not greater (i.e., #3b) than the screening PSA (#2) value, then an additional test for rising PSA (#4) will be required to document progression (Figure 2).

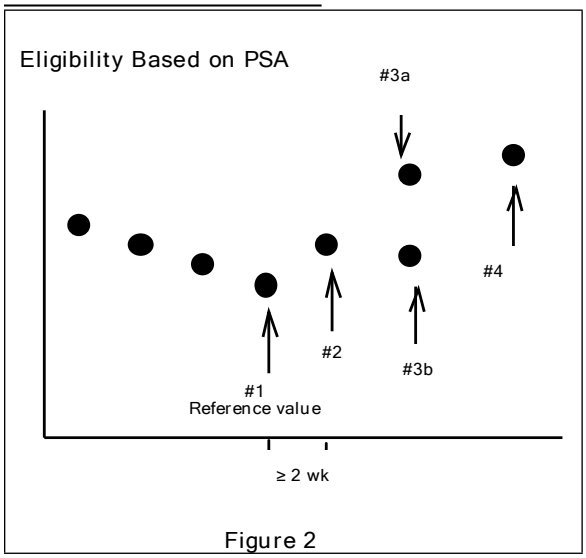


Figure 2

3) If no prior orchiectomy has been performed, patients must remain on LHRH agonist or antagonist (e.g. degarelix) therapy. Patients who are receiving an antiandrogen as part of primary androgen ablation must demonstrate disease progression following discontinuation of the antiandrogen, defined as two consecutive rising PSA values, obtained at least two weeks apart, or documented osseous or soft tissue progression. At least one of the PSA values must be obtained at least four weeks (flutamide) or six weeks (bicalutamide or nilutamide) after discontinuation.
4) Laboratory requirements:
    - Absolute neutrophil count (ANC) ≥ 1500/μL
    - Bilirubin < 1.5 x ULN
    - Hemoglobin ≥ 8 g/dL
    - PSA ≥ 2 ng/mL
    - Platelets ≥ 100,000/μL
    - AST and ALT ≤ 2.5 x ULN
    - Creatinine clearance ≥ 60mL/min by the Cockcroft Gault equation: (140 – age) x weight (kg)/(serum creatinine x 72)
    - Testosterone ≤ 50 ng/dL

5) Eastern Cooperative Oncology Group (ECOG) performance status 0 – 1 and life expectancy ≥ 12 weeks.
6) At least 18 years of age or older.
7) Patients receiving any other hormonal therapy, including any dose of megestrol acetate (Megace), Proscar (finasteride), or any systemic corticosteroid, must discontinue the agent for at least four weeks prior to ipilimumab treatment. Progressive disease as defined above must be documented after discontinuation of any hormonal therapy (with the exception of a LHRH agonist).
8) Prior radiation therapy must be completed ≥ 2 weeks prior to enrollment and the patient must have recovered from all toxicity. Prior radiopharmaceuticals (strontium, samarium, alpharadin) must be completed ≥ 4 weeks prior to enrollment.
9) Because of the unknown potential risk to a gamete and/or developing embryo from these investigational therapies, patients must agree to use adequate contraception (barrier method for males) for the duration of study participation, and for three months after discontinuing therapy.

4.2 Exclusion Criteria

1) Prior chemotherapy for metastatic CRPC. Prior neoadjuvant chemotherapy or chemotherapy for metastatic hormone sensitive prostate cancer are allowed so long as this treatment was completed at least 6 months prior to initiation of sipuleucel-T.
2) Prior treatment with an anti-CTLA-4 antibody treatment. The course of sipuleucel-T therapy (i.e. three treatments) leading up to this investigational trial must be the first course of therapy these patients have received.
3) Prostate cancer pain requiring regularly scheduled narcotics.
4) Current treatment with systemic steroid therapy (inhaled/topical steroids are acceptable). Systemic corticosteroids must be discontinued for at least 4 weeks prior to first treatment with ipilimumab.
5) History of autoimmune disease including, but not limited to:
    - Systemic lupus erythematosis (SLE), scleroderma, CREST syndrome, rheumatoid arthritis
    - Inflammatory bowel disease, celiac disease, primary biliary cirrhosis, autoimmune hepatitis
    - Dermatomyositis, polymyositis, giant cell arteritis
    - Autoimmune hemolytic anemia (AIHA), cryoglobulinemia, antiphospholipid antibody syndrome (APLS)
    - Diabetes mellitus type I, myasthenia gravis, Grave's disease
    - Wegener's granulomatosis or other vasculitis
    - A history of Hashimoto's thyroiditis, psoriasis, or eczema, any of which has been inactive for at least one year, or isolated Raynaud's phenomenon is acceptable
6) Known central nervous system or visceral metastases.

7) Medical or psychiatric illness that would, in the opinion of the investigator, preclude participation in the study or the ability of patients to provide informed consent for themselves.
8) Cardiovascular disease that meets one of the following: congestive heart failure (New York Heart Association Class III or IV), active angina pectoris, or recent myocardial infarction (within the last 6 months).
9) Concurrent or prior malignancy except for the following:
    - Adequately treated basal or squamous cell skin cancer
    - Adequately treated stage I or II cancer from which the patient is currently in complete remission
    - Any other cancer from which the patient has been disease-free for 5 years
10) Known HIV or other history of immunodeficiency disorder.
11) Prisoners or subjects who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or medical (e.g. infectious) illness.
12) Any underlying medical or psychiatric condition, which in the opinion of the investigator will make the administration of ipilimumab hazardous or obscure the interpretation of AEs, such as a condition associated with frequent diarrhea.

4.3 Removal of Subjects from Assessment

Subjects should remain on study and continue with protocol-specified tests and evaluations whenever possible. The Investigator may withdraw a subject from treatment or assessment at any time if, in his or her clinical judgment, it is in the best interest of the subject.

Subjects may discontinue their participation in the trial at any time without prejudice. If a subject chooses to withdraw early from the study, the Investigator should make every reasonable attempt to ensure that early withdrawal procedures are completed and to determine the reason for withdrawal. The date and reason for withdrawal will be recorded in the source documentation and on the CRF.

Patients will have monthly follow-up visits for 3-months after the last Ipilimumab dose and then Q 3 months until disease progression as defined in section 7.1.

4.3.1 Subject Follow-Up after Study Completion or Discontinuation

All AEs ongoing at the time of study completion or discontinuation that are considered by the Investigator to be clinically significant and related to study drugs will be followed until resolution, until the condition is deemed unlikely to improve, or until the subject is deemed lost to follow-up.

5 STUDY THERAPY

Sipuleucel-T is an autologous active cellular immunotherapy product designed to stimulate an immune response against prostate cancer. It consists of autologous peripheral blood mononuclear cells (PBMCs), including APCs that have been activated in vitro with a recombinant fusion protein composed of PAP, an antigen expressed in prostate adenocarcinoma,

linked to GM-CSF, an immune cell activator. A dose of sipuleucel-T is prepared from cells from a single leukapheresis procedure. each dose contains a minimum of 50 million autologous CD54+ cells activated with PAP-GM-CSF. Three planned doses of sipuleucel-T will be administered via IV infusion at 2-week intervals.

Following sipuleucel-T treatment, patients will receive ipilimumab either on the following day (immediate cohort) or 3 weeks later (delayed cohort). Ipilimumab is an anti human CTLA-4 monoclonal antibody. CTLA-4 interaction with the B7 molecule, one of its ligands expressed on antigen presenting cells, can down-regulate T-cell response. Ipilimumab is thought to act by blocking the interaction of CTLA-4 with the B7 ligand, resulting in a blockade of this immunologic checkpoint, thereby enhancing antigen-specific immune responses.

5.1 Sipuleucel-T (Provenge®, Dendreon Corporation)

Sipuleucel-T is an autologous cell product consisting of APCs loaded with prostate antigen PA2024. PA2024 is a recombinant fusion protein composed of PAP, an antigen expressed in prostate adenocarcinoma, linked to GM-CSF, an immune cell activator. Overall, immunohistochemistry and RNA probes suggest that PAP is generally an organ-specific prostate antigen and is highly expressed in normal and malignant prostate cells. However, there is evidence for expression of PAP in normal kidney cells, the islets cells of normal pancreas, and hair follicles [41,42]. The results from a quantitative polymerase chain reaction (PCR) study by Cunha et al. suggest that PAP transcript is expressed at low levels in several normal tissues [43]. They found low but detectable levels of mRNA, most notably in placenta, kidney, and testis. The kidney expression levels were 192-fold less than that seen in normal prostate tissue. The pancreas, small intestine, leukocytes, and to an even lesser degree, lung, ovary, colon, and spleen also exhibited very low but detectable levels of PAP transcripts. There are also reports in the literature suggesting that PAP is expressed in certain non-prostate-derived malignancies. For example, Wang et al. present immunohistochemical data that suggest PAP is expressed in colon, breast, and gastric tumors, but not the corresponding normal tissues [44].

The cDNA for PAP has been isolated. The analysis of sequence homology with other known proteins suggests 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.

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 research center for infusion.

Further information regarding the manufacture and characterization of sipuleucel-T is provided in the sipuleucel-T Investigator's Brochure.

5.1.1 Preparation of Sipuleucel-T

Leukapheresis and Collection of PBMCs

Subjects undergo a standard 1.5 to 2.0 total blood volume leukapheresis to harvest 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 manufacturing facility.

Quality Control 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.

Storage and Time Limitation

Sipuleucel-T should be maintained in the refrigerated shipping package until infused. The infusion of sipuleucel-T must begin prior to the expiration time indicated on the product label. Expired cell products must not be infused.

Chain of Identity

Because sipuleucel-T is an autologous blood product, access to subject identifying information is critical to ensure subject safety. To maintain the chain of identity and thereby ensure subject safety, a label that contains subject identifying information accompanies the product. This label is completed by medical personnel performing the leukapheresis procedure. The subject-specific label will accompany the cell product throughout the manufacturing process and will accompany the cell product to the study center. Therefore, the subject's identifying information will be revealed to manufacturing facility staff and to Dendreon's manufacturing department.

Infusion - Sipuleucel-T is to be administered per institutional guidelines (suggestions below)

Subjects will be premedicated with acetaminophen and an antihistamine such as diphenhydramine prior to each infusion of sipuleucel-T. The infusion will be administered over approximately 30 to 60 minutes through an IV line suitable for blood transfusion (without a cell filter). Common treatment-emergent AEs, such as pyrexia, chills, fatigue, nausea, and joint ache and/or rigors, may warrant reduction of the infusion rate.

In the event of an acute infusion reaction, the infusion may be interrupted or slowed, depending on the severity of the reaction. Appropriate medical therapy should be administered as needed. In controlled clinical trials, symptoms of acute infusion reactions were treated with acetaminophen, intravenous H1 and/or H2 blockers, and low dose intravenous meperidine. If the infusion of sipuleucel-T must be interrupted, the infusion should not be resumed if the sipuleucel-T infusion bag will be held at room temperature for more than 3 hours.

Subjects will be observed for at least 30 minutes following the infusion.

5.2 Ipilimumab (Yervoy®, BMS)

Ipilimumab is a human monoclonal antibody specific for the CTLA-4 antigen expressed on a subset of activated T-cells. CTLA-4 interaction with the B7 molecule, one of its ligands expressed on antigen presenting cells, can down-regulate T-cell response. Ipilimumab is thought to act by blocking the interaction of CTLA-4 with the B7 ligand, resulting in a blockade of the inhibitory effect of T-cell activation that is created by the CTLA-4/B7 interaction.

5.2.1 Dose Calculations

Ipilimumab dosing will be based on actual weight All patients will receive ipilimumab 3 mg/kg dosed IV over 90 minutes every 3 weeks for 4 doses as induction treatment. In the event that a patient responds to treatment, and then subsequently progress, the patient may receive reinduction treatment.

5.2.2 Provision of Drug

Ipilimumab is supplied by the study in single-use, glass vials as a sterile, colorless solution for intravenous administration containing 200 mg or 50 mg.

5.3 Dose Modifications

5.3.1 Sipuleucel-T Modifications

A subject may not receive all 3 infusions of sipuleucel-T if any of the following occurs prior to completion of the treatment regimen:

- The subject develops an unacceptable toxicity (defined as ≥ National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade 3 toxicity) deemed by the Investigator as possibly or probably related to infusion with sipuleucel-T, with the exception of the following Grade 3 events: pyrexia, fatigue, asthenia;
- The subject develops a concurrent illness that prevents further administration of sipuleucel-T;
- The subject elects not to receive all 3 infusions of sipuleucel-T or withdraws consent;
- It is determined that it is not possible to manufacture sipuleucel-T that will pass QC testing;
- At the discretion of the Investigator.

Subjects who receive fewer than 2 infusions of sipuleucel-T due to any of the reasons noted above will continue to be followed for 12 weeks, but will not be randomized for ipilimumab treatment and will be replaced.

Patients are randomized after the second sipuleucel-T infusion. If the second infusion cannot be administered, then the patient will not be randomized and will be replaced. This will not affect the evaluation of the primary study aim. If the patient is randomized but does not receive the third sipuleucel-T infusion for any of the reasons listed above, this patient will be replaced. The frequency of such an occurrence will be monitored. Patients must receive 3 doses of sipuleucel-T over a maximum of 10 weeks in order to continue in the study and receive ipilimumab.

5.3.2 Ipilimumab Modifications

Ipilimumab doses that cannot be given on schedule due to treatment-related adverse events will be skipped. No dose adjustments or delay will be allowed for treatment-related adverse events. Decisions to skip an ipilimumab dose must be made on specified safety criteria. Treatment with ipilimumab will be skipped or discontinued if the subject experiences at least one adverse event, specified below, considered by the investigator to be "possibly", probably" or "definitely" related to ipilimumab treatment.

Study drug dosing will be skipped for the following treatment-related adverse event(s):

- Any ≥ Grade 2 non-skin, treatment-related adverse event (including irAEs), except for laboratory abnormalities
- Any ≥ Grade 3 treatment-related laboratory non-hematologic abnormality
- Any adverse event, laboratory abnormality or intercurrent illness that, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued dosing

It is necessary to skip study drug dosing for the following adverse events:

- Any ≥ Grade 3 skin related adverse event regardless of causality

Restart ipilimumab dosing if/when the adverse event(s) resolve(s) to ≤ Grade 1 severity or returns to baseline within 2 weeks of the last ipilimumab dose:

If the *adverse event has resolved,* restart ipilimumab dosing at the next scheduled time point per protocol.

If the adverse event has not resolved in time for the next dose (3 weeks ±3 days), the next scheduled dose will be skipped and dosing will be resumed at the subsequently scheduled dose. *Withhold of ipilimumab for longer than 60 days after the scheduled dose will lead to permanent discontinuation. Toxicities, which cause dosing delays > 60 days will be considered sufficiently serious to lead to permanent discontinuation (not allowing for re-induction).*

If > 1 dose is expected to be skipped, the dosing schedule modifications must be discussed with the principal investigator prior to implementation.

5.4 Management of Toxicity

5.4.1 General Guidelines for Managing Toxicity

For ipilimumab, dose skipping should occur for any toxicity ≥ grade 3 that is determined to be possibly, probably or definitely related to either of the study drugs. Please refer to the AE Management Algorithms provided in the Investigator Brochure for guidance on management of potentially ipilimumab-related adverse events. Toxicities must have resolved to ≤ grade 1 before resuming therapy.

5.4.2 Hypersensitivity Reactions

Since ipilimumab contains only human protein sequences, it is less likely that any allergic reaction will be seen in patients. However, it is possible that infusion of ipilimumab will induce a cytokine release syndrome that could be evidenced by fever, chills, rigors, rash, pruritus, hypotension, hypertension, bronchospasm, or other symptoms. No prophylactic pre-medication will be given unless indicated by previous experience in an individual patient. Reactions should be treated based upon the following recommendations or per institutional protocol.

For mild symptoms (e.g., localized cutaneous reactions such as mild pruritus, flushing, rash):

- Decrease the rate of infusion until recovery from symptoms, remain at bedside and monitor patient.
- Complete the ipilimumab infusion at the initial planned rate.
- Diphenhydramine 50 mg IV may be administered at the discretion of the treating physician and patients may receive additional doses with close monitoring.
- Premedication with diphenhydramine may be given at the discretion of the investigator for subsequent doses of ipilimumab.

For moderate symptoms (any symptom not listed above as mild symptoms; or below as severe symptoms, such as generalized pruritus, flushing, rash, dyspnea, and hypotension with systolic BP >80 mmHg):

- Interrupt ipilimumab.
- Administer diphenhydramine 50 mg IV.
- Monitor patient closely until resolution of symptoms.
- Corticosteroids may abrogate any beneficial immunologic effect, but may be administered at the discretion of the treating physician.
- Resume ipilimumab infusion after recovery of symptoms.
- At the discretion of the treating physician, ipilimumab infusion may be resumed at *one half the initial infusion rate, then increased incrementally to the initial infusion rate.* If symptoms develop after resumption of the infusion, the infusion should be discontinued and no additional ipilimumab should be administered that day.
- The next dose of ipilimumab will be administered at its next scheduled time and may be given with pre-medication (diphenhydramine and acetaminophen) and careful monitoring, following the same treatment guidelines outlined above. At the discretion of the treating physician additional oral or IV antihistamine may be administered prior to dosing with ipilimumab.

For severe symptoms (e.g., any reaction such as bronchospasm, generalized urticarial, systolic blood pressure < 80 mm Hg, or angioedema):

- Immediately discontinue infusion of ipilimumab, and disconnect infusion tubing from the subject.

- Consider bronchodilators, epinephrine 1 mg IV or subcutaneously, and/or diphenhydramine 50 mg IV, with solumedrol 100 mg IV, as needed.
- Patients should be monitored until the investigator is comfortable that the symptoms will not recur.
- No further ipilimumab will be administered.

In case of late-occurring hypersensitivity symptoms (e.g., appearance within one week after treatment of a localized or generalized pruritus), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

5.4.3 Management of Hepatotoxicity

Liver function tests (AST, ALT, T. bilirubin) will be evaluated for every subject prior to administration of ipilimumab. Blood samples must be collected and analyzed at local or central labs within 3 days prior to dosing. LFT results must be reviewed by the principal investigator (or designee) to meet dosing criteria specifications: ≤ 2.5 x ULN for AST, ALT and ≤ 1.5 x ULN for T. bilirubin unless liver metastases are present in which case LFT ≤ 5 x ULN for AST, ALT and T. bilirubin ≤ 3.0 x ULN) prior to dosing.

If, during the course of treatment abnormal LFT values are detected, the subject must be managed using the hepatotoxicity algorithm section in the appendix.

5.4.4 Treatment of Ipilimumab-Related Isolated Drug Fever

In the event of isolated drug fever, the investigator must use clinical judgment to determine if the fever is related to the ipilimumab or to an infectious etiology. If a patient experiences isolated drug fever, for the next dose, pre-treatment with acetaminophen or non-steroidal anti-inflammatory agent (investigator discretion) should be instituted and a repeated antipyretic dose at 6 and 12 hours after ipilimumab infusion, should be administered. The infusion rate will remain unchanged for future doses. If a patient experiences recurrent isolated drug fever following premedication and post dosing with an appropriate antipyretic, the infusion rate for subsequent dosing should be decreased to 50% of the previous rate. If fever recurs following infusion rate change, the investigator should assess the patient's level of discomfort with the event and use clinical judgment to determine if the patient should receive further ipilimumab.

5.4.5 Immune Related Toxicity

Blocking CTLA-4 function may permit the emergence of auto-reactive T cells and resultant clinical autoimmunity. Rash/vitiligo, diarrhea/colitis, uveitis/episcleritis, hepatitis, and hypopituitarism were drug-related, presumptive autoimmune events, now termed irAEs, noted in previous ipilimumab studies.

For the purposes of this study, an irAE is defined as an AE of unknown etiology associated with drug exposure and consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an AE an irAE. Serological, immunological, and histological (biopsy) data should be used to support the diagnosis of an immune-mediated toxicity. Suspected irAEs must be documented on an AE or SAE form.

Patients should be informed of and carefully monitored for evidence of clinically significant systemic irAE (e.g., systemic lupus erythematosus-like diseases) or organ-specific irAE (e.g., rash, colitis, uveitis, hepatitis or thyroid disease). If an irAE is noted, appropriate work-up (including biopsy if possible) should be performed, and steroid therapy may be considered if clinically necessary.

It is unknown if systemic corticosteroid therapy has an attenuating effect on ipilimumab activity. However, clinical anti-tumor responses have been maintained in patients treated with corticosteroids and discontinued from ipilimumab. If utilized, corticosteroid therapy should be individualized for each patient. Prior experience suggests that colitis manifested as ≥ Grade 3 diarrhea requires corticosteroid treatment.

The most common immune-related adverse events are dermatologic, endocrine, gastrointestinal, and hepatic. For any suspected immune-related adverse event, begin with the algorithm in the Appendix. For diarrhea, hepatotoxicity, or endocrinopathy, this will refer the investigator to a more specific algorithm (see Appendix). For rash, see the below.

Skin related AE

Fatal toxic epidermal necrolysis (TEN) has been reported following a grade 3 skin-related AE, which was considered unrelated to ipilimumab on a Bristol-Myers Squibb-sponsored trial. In patients with a **drug-related** Grade 2 skin immune-mediated toxicity or Grade 3 skin-related adverse event, **regardless of causality**, additional treatment will be delayed until the event improves to ≤ Grade 1 severity.

In patients with **drug-unrelated** grade 2 skin-related adverse events, no dosing delay is required. Patient with a Grade 1 skin AE, **regardless of causality**, are to be treated per institutional guidelines.

A dermatologist should evaluate persistent or severe rash or pruritus. A biopsy should be performed if appropriate and if possible, photos of the rash should also be obtained. Low grade ipilimumab-mediated rash and pruritus were treated with symptomatic therapy (e.g., antihistamines). Topical or parenteral corticosteroids may be required for more severe symptoms. With the appearance of any generalized rash, concomitant medications (e.g.. antibiotics, anticonvulsants, or proton pump inhibitors) that may be associated with severe skin reactions (e.g., Stevens Johnson Syndrome, TEN) should be discontinued and avoided. Ipilimumab should also be held.

Specific treatment algorithms for immune-related adverse events are included as appendices to this protocol.

5.4.6 Discontinuation of Ipilimumab Treatment

The following treatment-related non-neurological adverse events require permanent discontinuation of ipilimumab:

- Any ≥ Grade 2 eye pain or reduction of visual acuity that does not respond to topical therapy and does not improve to ≤ Grade 1 severity within 2 weeks of starting therapy, OR requires systemic treatment.
- Any ≥ Grade 3 bronchospasm or other hypersensitivity reaction.

- Any other ≥ Grade 3 non-skin related adverse event with the exception of events listed below under "Exceptions to Permanent Discontinuation".
- Any ≥ Grade 4 laboratory abnormalities, except AST, ALT, or Total Bilirubin
- AST or ALT > 5 x ULN
- Total Bilirubin > 3 x ULN
- Any other ≥ Grade 4 adverse event
- *Withhold of ipilimumab for greater than 60 days due to treatment related toxicity*
- Any adverse event, laboratory abnormality or intercurrent illness, which, in the judgment of the investigator, presents a substantial clinical risk to the patient with continued dosing.
- The development of progression in the global tumor burden and/or clinical deterioration of subject's condition such that further benefit from ipilimumab dosing is unlikely or requires a change of therapy.

The following neurological adverse event requires permanent discontinuation of ipilimumab and defines unacceptable neurotoxicity:

- Any motor neurologic toxicity ≥Grade 3 regardless of causality
- Any ≥ Grade 3 treatment related sensory neurologic toxicity

Please refer to the Appendices for specific treatment algorithms.

5.4.6.1 Exceptions to Permanent Discontinuation

- Potentially reversible inflammation (< Grade 4), attributable to a local anti-tumor reaction and a potential therapeutic response. This includes inflammatory reactions at sites of tumor resections or in draining lymph nodes, or at sites suspicious for, but not diagnostic of metastasis.
- Hospitalization for ≤ Grade 2 adverse events where the primary reason for hospitalization is to expedite the clinical work-up.
- Patients with the following conditions where in the investigator's opinion continuing study drug administration is justified:
  - Ocular toxicity that has responded to topical therapy.
  - Endocrinopathies where clinical symptoms are controlled with appropriate hormone replacement therapy. **Note:** Ipilimumab may not be restarted while the patient is being treated with systemic corticosteroids except for patients on stable doses of hormone replacement therapy such as hydrocortisone.

5.5 Prohibited Therapies During the Study

Patients in this study may not use vaccines for the treatment of cancer or prevention of disease unless indicated as a component of the protocol regimen (including those for common medical

conditions) for up to one month pre- and post-dosing with ipilimumab. Concomitant systemic or local anti-cancer medications or treatments are prohibited in this study while receiving ipilimumab treatments. Bone targeted agents (e.g. zolendronate, denosumab) are allowed.

Patients may not use any of the following therapies during the study:

- Any non-study anti-cancer agent (investigational or non-investigational)
- Any other investigational agents
- Any other (non-CA184024 related) CTLA-4 inhibitors or agonists
- Immunosuppressive agents
- Chronic systemic corticosteroids

Patients should receive full supportive care, including transfusions of blood and blood products, erythropoietin, antibiotics, antiemetics, etc., when appropriate. Treatment with hormones or other chemotherapeutic agents may not be administered except for hormones administered for non-disease-related conditions (e.g., insulin for diabetes mellitus) and continued LHRH agonist therapy. Palliative radiation therapy may not be administered during protocol treatment. No steroids, except as directed by the protocol, for immune events or for severe hypersensitivity reactions, are allowed.

6 STUDY PROCEDURES AND OBSERVATIONS

The Study Calendar summarizes the frequency and timing of various measurements.

6.1 Study Calendar

	Pre-study				Treatment						Follow Up
Evaluation or Treatment	Proven ge 1	Proven ge 2	Proven ge 3	Pre-Ipilimumab	**Day 1** [a] +/- 3 days	**Day 22** +/- 3 days	**Day 43** +/- 3 days	**Day 64** +/- 3 days	**Day 85** +/- 3 days	Monthly for 3 months, then Q3 months[i]	Off Study
Arm 1: Immediate Ipilimumab [b]					X	X	X	X			
Sipuleucel-T	X	X	X								
Arm 2: Delayed Ipilimumab [b]						X	X	X	X		
Sipuleucel-T	X	X	X								
Informed Consent				X							
Physical Exam				X		X	X	X	X	X	X
Medical History				X							
Height				X							
Weight				X		X	X	X	X	X	X
Concomitant Medications				X		X	X	X	X	X	X
Toxicity Assessment				X		X	X	X	X	X	X
Performance Status				X		X	X	X	X	X	X
CBC w/diff, platelets				X		X	X	X	X	X	X

6.1 Study Calendar

	Pre-study				Treatment						Follow Up
Evaluation or Treatment	Provenge 1	Provenge 2	Provenge 3	Pre-Ipilimumab	**Day 1** [a] +/- 3 days	**Day 22** +/- 3 days	**Day 43** +/- 3 days	**Day 64** +/- 3 days	**Day 85** +/- 3 days	Monthly for 3 months, then Q3 months[i]	Off Study
Serum chemistry [c]				X		X	X	X	X	X	X
PSA				X	X	X	X	X	X	X	X
Urinalysis w/ micro				X		X	X	X	X		
Testosterone				X							
TSH, free T4				X	X	X	X	X	X	X	X
Blood for immune monitoring (all patients) [d]				X	X[j]	X	X	X	X	X	X
CT/MRI & Bone scan [f, g]				X [e]					X	X	
Immune Worksheet [h]				X	X	X	X	X	X	X	X
Cortisol stimulation test				X							
Archived tumor tissue (if available)				X							

[a.] Pre-study clinical (physical exam and performance status) and laboratory parameters are to be measured within 15 days of beginning treatment (unless otherwise indicated in section 6.2.1.1) and do not need to be repeated on Day 1.

[b.] Patients randomized to Arm 1 will begin treatment with Ipilimumab 1-3 business days following the last Provenge infusion. Day 1 of the trial will be designated as the day the patient receives the first dose of ipilimumab. For patients randomized to Arm 2, Day 1 will be determined following the same parameters as Arm 1 (1-3 business days following the final Provenge infusion), with Day 22 designated as the day the patient receives the first dose of Ipilimumab

[c.] SGOT, SGPT, alk phos, total bili, LDH, electrolytes (Na, K, CO_2, Cl), glucose, BUN, Cr, amylase, lipase.

[d.] 60 mL in a green top tube will be collected from all patients and shipped/delivered by the Clinical Research Coordinator to Dr. Lawrence Fong's laboratory (513 Parnassus Ave, Room HSE 301, SF, CA 94143) for the ELISA and ELISPOT immune assays. Blood must be drawn pre-treatment. Please refer to the Lab Manual for shipping instructions for blood.

e. Pre-study radiographic staging is to be measured within 8 weeks of beginning treatment.
f. CT/MRI abd/pelvis is at baseline. If metastatic disease is suspected elsewhere, other imaging modalities (e.g. CT chest) are accepted to demonstrate progressive disease for eligibility. This imaging should continue with protocol-required scans throughout study participation, as indicated. If soft tissue metastatic disease is found at baseline, scans will be repeated at day 85 (+/- 7 days) and every 12 weeks (+/- 7 days) thereafter. Can also be done more often if clinically indicated.
g. Bone scans are at baseline, day 85 (+/- 7 days), and every 12 weeks (+/- 7 days) until PD is reached; can be more often if clinically indicated.
h. Every Clinic visit will include clinical monitoring for clinical autoimmunity as outlined in Appendix 2.
i. Q3month follow-up visits should continue until PD or 2 years, whichever comes first.
j. Blood for Immune Monitoring does not need to be repeated on Day 1 if drawn within 15 days of Day 1.

6.2 Procedures by Visit

6.2.1 Study Procedures by Visit and Treatment Cycle

Note that results of all safety laboratory tests (all chemistry and all hematology results) must be obtained and reviewed before ipilimumab administration, as applicable. All laboratory results must be within the established range before ipilimumab is administered. Laboratory evaluations using a local laboratory must be performed and the result examined by the investigator before administration of each dose of ipilimumab.

6.2.1.1 Screening/Baseline Visit (within 15 days of Cycle 1 Day 1, unless otherwise indicated)

- Informed consent (can occur any time pre-ipilimumab)
- Physical Exam including height, weight
- Medical history and concomitant medication review
- Performance Status evaluation
- Laboratory Tests: CBC with differential and platelets, serum chemistry (SGOT, SGPT, alk phos, total bili, LDH, electrolytes (Na, K, CO_2, Cl), glucose, BUN, Cr, amylase, lipase), PSA,
    - Within 28 days of Cycle 1 Day 1: Testosterone, TSH, free T4.
- Cortisol stimulation test
- Urinalysis with micro (within 28 days of Cycle 1 Day 1)
- CT abdomen/pelvis with contrast and Bone Scan (within 8weeks of Cycle 1 Day 1)
- Archived tumor tissue (if available)
- Immune monitoring – all patients at UCSF and MD Anderson (can occur any time after signing consent)
- Immune worksheet

6.2.1.2 Treatment Visits

All patients will receive SipT treatment (leukapherisis and infusion) every 2 weeks. The leukapherisis and infusion appointments are scheduled 2 to 3 days apart, and can start on various days of the week. The final infusion dose of SipT (Day 0) is usually about 30 days from the date of first dose.

All patients will receive ipilimumab 3 mg/kg IV on Day 1 of each 21-day cycle. Laboratory assessments listed below may be performed +/- 3 days from Day 1 in order to allow for the collection and review of results prior to dosing.

Day 1 of Induction Cycles 1-4 (+/- 3 days)
Pre-study clinical physical exam, performance status, and laboratory parameters, including Immune Monitoring, are to be measured within 15 days of beginning treatment and do not need to be repeated on Cycle 1 Day 1.

- Physical Exam, including weight
- Toxicity and concomitant medications assessment
- Performance Status assessment
- Laboratory Tests: CBC with differential and platelets, serum chemistry (SGOT, SGPT, alk phos, total bili, LDH, electrolytes, glucose, BUN, Cr, amylase, lipase), PSA
- Immune monitoring – all patients at UCSF and MD Anderson
- Additional immune monitoring – MD Anderson patients ONLY
- TSH, T4 (beginning at Cycle 2 Day 1 – Study Day 22)
- Urinalysis with micro
- Immune worksheet

Bone scans will be performed every 12 weeks during induction treatment, or when clinically indicated, and at disease progression. CT scans will be performed every 12 weeks only if baseline scan is indicative of metastatic disease; or if otherwise clinically indicated.

6.2.1.3 Follow-up Visits

Patients will have monthly visits for 3 months following the last dose of ipilimumab. The following assessments will be performed at this visit:

- Physical Exam, including weight
- Toxicity and concomitant medications assessment
- Performance Status assessment
- Laboratory tests: CBC with differential and platelets, serum chemistry (SGOT, SGPT, alk phos, total bili, LDH, electrolytes, glucose, BUN, Cr, amylase, lipase), PSA, TSH, T4
- Immune monitoring – all patients at UCSF and MD Anderson
- Additional immune monitoring – MD Anderson patients ONLY
- Immune worksheet

6.2.2 Study Completion or Early Discontinuation Visit

Patients will continue on therapy, including any re-induction therapy, until any one of the following events occurs:

- Progressive disease, as defined in section 7.1
- Patient withdraws consent
- Treating physicians' discretion

For all patients without significant AEs, PSA and/or objective progression will not require the patient to come off study until at least three cycles of therapy have been administered.

Patients may choose to withdraw at any time. No further protocol therapy will subsequently be given. At the time of study early withdrawal, the reason for early withdrawal and any new or continuing adverse events should be documented.

6.2.3 Study Drug Discontinuation

If study drug administration is discontinued, the reason for discontinuation will be recorded. Patients will return for a 30 day follow up visit (± 5 days) as described in section 6.2.1.c.

Subjects MUST be discontinued from study therapy AND withdrawn from the study for the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued treatment with study therapy is not in the best interest of the subject
- Pregnancy: Partners of WOCBP should be instructed to contact the investigator immediately if they suspect their partner might be pregnant (e.g., missed or late menstrual period) at any time during study participation. The investigator must immediately notify BMS in the event of a confirmed pregnancy in a partner participating in the study.
- Termination of the study by Bristol-Myers Squibb (BMS) and/or Dendreon.
- Imprisonment or the compulsory detention for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

7 EFFICACY AND SAFETY ASSESSMENTS

7.1 Efficacy Assessment

7.1.1 Immune Response Endpoints

The primary immune study hypothesis is to assess the frequency of observing an IgG antibody response to PAP and/or PA2024 at baseline and at week 20 for each of the two ipilimumab schedules. The IgM and IgG antibody responses to PAP and PA2024 will both be assessed with an ELISA assay at baseline and week 20 after the start of protocol therapy. T cell responses to PAP and PA2024 will be assessed with an ELISPOT assay at baseline and at week 20 after the start of protocol therapy.

7.1.2 Clinical Response Endpoints

Ipilimumab is expected to trigger immune-mediated responses, which require activation of the immune system prior to the observation of clinical responses. Such immune activation may take weeks to months to be evident. Some patients have had objective volume increase of tumor lesions or other disease parameters within 12 weeks following the start of ipilimumab, which is

subsequently followed by objective clinical responses [9,45]. Early in the treatment, patients may not have had sufficient time to develop the required immune activation or, in some patients, tumor volume or other disease parameter increases may represent infiltration of lymphocytes into the original tumor or blood. In conventional studies, such tumor volume or relevant laboratory parameter increases during the first 12 weeks of the study would constitute PD and lead to discontinuation of treatment as well as subsequent imaging to detect response, thus disregarding the potential for subsequent immune-mediated clinical response.

Therefore, patients with tumor volume increase detected or lack of laboratory parameter response documentation prior to week 12 but without rapid clinical deterioration should continue on treatment with ipilimumab and continue to be imaged to allow detection of a subsequent tumor response. This will improve the overall assessment of the clinical activity or ipilimumab and will more likely capture its true potential to induce clinical responses. Clinical assessment will be made using PSA response and radiographic response using standard irRC.[9]

7.1.3 Clinical Efficacy Evaluation

Patients will have PSA measurements on day 1 of every cycle prior to treatment. PSA decline will be evaluated according to the recommendations from PSA Working Group (PSAWG)[39]. Although response in this study is defined as a PSA decline, progressive disease is defined as progression by either PSA or objective progression. Bone scans and CT scans will be repeated every 12 weeks and at the time of PSA progression. Each category (measurable, non-measurable, and PSA) will be assessed and reported independently. Measurable disease/target lesions and non-measurable disease/non-target lesions will be evaluated according to the irRC. [9]

7.1.3.1 Definition of PSA Decline

All patients, with or without measurable disease, will be evaluated for PSA decline.

Patients with disease that is not measurable will be eligible for this study and will be assessed for response based on changes in PSA and serial bone scans. The baseline serum PSA must be at least 2 ng/mL.

30% PSA Decline: PSA decline of at least 30% from baseline confirmed by a second measurement at least 4 weeks later. The reference for these declines should be a PSA measured within 2 weeks prior to starting therapy.

50% PSA Decline: PSA decline of at least 50% from baseline confirmed by a second measurement at least 4 weeks later. The reference for these declines should be a PSA measured within 2 weeks prior to starting therapy.

PSA Progression: If at least a 50% PSA decline has been achieved, PSA progression occurs when the PSA has increased to 25% above the nadir and the increase in the absolute-value PSA level is at least 2 ng/mL, or back to baseline, whichever is lower, on at least 2 consecutive measurements at least 1 weeks apart. For patients without a PSA decline of this magnitude, or without any decline in PSA, progression will be defined by a 25% increase over baseline or nadir PSA (whichever is lower) and an increase in the absolute value PSA level by at least 2 ng/mL, on at least 2 consecutive measurements, after 12 weeks of therapy. For all patients without SigAEs, PSA and/or objective progression will not require the patient to discontinue study treatment until at least three cycles of therapy have been administered.

PSA Decline Duration: The PSA decline duration commences on the date of the first 50% decline in PSA. The response duration ends when the PSA value increases by 50% above the nadir, provided that the increase in the absolute-value PSA level is at least 2 ng/mL or back to baseline, whichever is lower. If a patient does not progress for the duration of the study, his data will be censored at the time of last PSA follow-up.

Progressive Disease: Defined by PSA progression or by objective progression (based on RECIST 1.1 criteria or the appearance of two or more new lesions on bone scan, confirmed 6 or more weeks later) more than three months after the initiation of therapy. Although response in this study is defined as a PSA decline, progressive disease is defined as progression by either PSA or objective progression.

Time to PSA Progression: The start of the time to PSA progression is the day treatment is initiated. The end date is the time of PSA progression as defined above. If a patient does not progress for the duration of the study, his data will be censored at the time of last PSA follow-up.

7.1.3.2 Definition of Measurable and Non-Measurable Lesions

Measurable Disease/Target Lesions

All measurable lesions (lesions that can be accurately measured in at least one dimension, longest diameter to be recorded, as ≥10 mm with spiral CT) up to a maximum of 5 lesions per organ and 10 lesions total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and the suitability for accurate repeated measurements (either by imaging techniques or clinically). The sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (5 lesions per organ, up to 10 visceral lesions) is calculated. At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (≥5 × 5 mm; up to 5 new lesions per organ and 10 visceral lesions) are added together to provide the total tumor burden:

$$\text{Tumor Burden} = \text{SPD}_{\text{index lesions}} + \text{SPD}_{\text{new, measurable lesions}}.$$

The overall response according to the irRC is derived from time-point response assessments (based on tumor burden) as follows:

- Complete Response (CR): complete disappearance of all lesions (whether measurable or not, and no new lesions)
  - confirmation by a repeat, consecutive assessment no less than 4 wks from the date first documented
- Partial Response (PR), decrease in tumor burden ≥50% relative to baseline
  - confirmed by a consecutive assessment at least 4 wks after first documentation
- Stable Disease (SD), not meeting criteria for CR or PR, in absence of PD
- Progressive Disease (PD), increase in tumor burden ≥25% relative to nadir (minimum recorded tumor burden)
  - confirmation by a repeat, consecutive assessment no less than 4 wks from the date first documented

Patients were considered to have PR or SD even if new lesions were present, as long as they met the respective thresholds of response as described above. Furthermore, patients were not considered to have PD if new lesions were present and the tumor burden of all lesions did not increase by ≥25%. In contrast to CR, PR, and PD, a response of SD does not require confirmation. It is important to note that CR, PR, and SD include all patients with CR, PR, or SD by WHO criteria as well as those patients that shift to these irRC categories from WHO PD. Patients with SD, particularly those with slow-declining tumor burden ≥25% from baseline at the last tumor assessment, are considered clinically meaningful because they show an objectively measurable reduction in tumor burden without reaching the 50% threshold that defines PR (it represented an objectively measured reduction not commonly observed in the natural history of advanced melanoma patients).

Confirmation: To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat studies no less than 4 weeks after the criteria for response are first met

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

Non-measurable Disease/Non-Target Lesions

All non-measurable lesions (including small lesions, longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan and truly non-measurable lesions such as bone lesions) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Complete Response (CR): The disappearance of all non-target lesions

Incomplete Response/Stable Disease (IR/SD): The persistence of one or more non-target lesion(s) without unequivocal progression of existing non-target lesions

Progressive Disease (PD): The appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. For bone scans, the appearance of 2 or more new lesions is required. These lesions should be re-evaluated 6 or more weeks later to confirm progressive disease. Increased intensity of uptake in previously abnormal areas on bone scans is not considered progressive disease, unless the lesions seen on the correlative imaging studies performed of this area meet the criteria for progression.

7.2 Safety Assessments

All patients who receive at least one dose of ipilimumab will be considered evaluable for safety parameters. Additionally, any occurrence of non-serious or SAE from time of consent forward, up to and including follow-up visits, will be reported.

Safety will be evaluated for all treated patients using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4 (http://ctep.cancer.gov). Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, physical examinations, and clinical laboratory tests.

7.3 Adverse Event Reporting

An adverse event (also known as an adverse experience) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. More specifically, an adverse event (can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

7.3.1 Serious Adverse Events

A ***serious adverse event (SAE)*** is any untoward medical occurrence that at <u>any dose</u>:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see "note" below for exceptions)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- Suspected transmission of an infectious agent (e.g., any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE.
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Although overdose and cancer are not always serious by regulatory definition, these events should be reported on an SAE form and sent to BMS in an expedited manner. An overdose is defined as the accidental or intentional ingestion or infusion of any dose of a product that is considered both excessive and medically important.

NOTE: The following hospitalizations are <u>not</u> considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department for less than 24 hours that does not result in admission (unless considered an "important medical event" or a life-threatening event)
- elective surgery, planned before signing consent
- admissions as per protocol for a planned medical/surgical procedure

- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

Note that all pregnancies, regardless of outcome, must be reported to the sponsor on a Pregnancy Surveillance Form, not an SAE form. All pregnancies must be reported and followed to outcome, including pregnancies that occur in the female partner of a male study subject. **See Section 7.5.3 for instructions on reporting pregnancies.**

Following the subject's written consent to participate in the study, all SAEs must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 70 days of discontinuation of dosing of the investigational product. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy). The investigator should notify BMS and Dendreon of any SAE occurring after this time period that is believed to be related to the investigational product or protocol-specified procedure.

All SAEs whether related or unrelated to the ipilimumab, must be immediately reported to BMS and Dendreon (by the investigator or designee) within 24 hours of becoming aware of the event. If only limited information is initially available, follow-up reports are required. The original SAE form must be kept on file at the study site. If the SAE occurs at a Participating Institution, the Lead Site must also be notified.

If an ongoing SAE changes in its intensity or relationship to the investigational product, a follow-up SAE report should be sent immediately to the sponsor. As follow-up information becomes available it should be sent immediately using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization.

7.3.2 Significant Adverse Events

An understanding of the expected toxicities of ipilimumab suggests that the definition of "significant adverse events" (SigAEs) should exclude manageable immune related adverse events (irAEs). However, IrAEs refractory to steroid treatment will also be considered SigAEs. To evaluate the frequency of immune toxicities, patients will be assessed at baseline and monthly for immune signs and symptoms.

Significant Adverse Event (SigAE) is defined by any of the following that are attributable to therapy:

- Any ≥ grade 3 or 4 non-immune-mediated toxicity (with immune-mediated toxicities defined as all irAEs listed in the ipilimumab investigators' brochure to be considered immune and per judgment of the principal investigator for events unknown as immune related adverse events).

- Any ocular toxicity considered to be immune-mediated and requiring systemic steroids.
- Any grade 3 or 4 irAEs that cannot be reduced to grade 2 or below with systemic steroids.

The following events are excluded as SigAE:

- Any toxicity attributable to androgen deprivation therapy.
- Any endocrinopathy thought to be immune-mediated where clinical symptoms are controlled with appropriate hormonal replacement therapy.
- Hospitalization for ≤ grade 2 events where the reason for hospitalization is to expedite evaluation rather than to treat the toxicity.
- These criteria apply for both hematologic and non-hematologic toxicities.
- Grade 4 laboratory-only abnormalities for uric acid, WBC, and components of the WBC count.

7.4 Assignment of Adverse Event Intensity and Relationship to Investigational Product

The following categories and definitions of causal relationship to investigational product as determined by a physician should be used:

- **Unrelated:** The cause of the AE is known and the event is in no way related to any aspect of study participation. If there is any uncertainty regarding AE causality then the event must be assessed as possibly related to research participation and reported to the IRB as indicated. Often, the cause of an unrelated AE is disease progression.
- **Possibly Related:** An AE is possibly related when there is a reasonable possibility that the event might have been caused by study participation. A possibly related event may follow no known pattern of response and an alternative cause seems more likely. In other circumstances there may be significant uncertainty about the cause of the event, or a possible relationship to study participation cannot reasonably be ruled out.
- **Probably Related:** An AE is probably related when there is a reasonable possibility that the event is likely to have been caused by study participation. The AE has a timely relationship to the study procedure(s) and follows a known pattern of response, but a potential alternative cause may be present.
- **Definitely Related:** An AE is definitely related to study participation if it is clear that the event was caused by study participation. A definitely related event has a strong temporal relationship and an alternative cause is unlikely.

7.5 Collection and Reporting

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. The following information should be captured for all AEs: onset, duration, intensity, seriousness, relationship to investigational product, action taken, and treatment required. If treatment for the AE was administered, it should be recorded in the medical record.

The investigator shall supply the sponsor and Ethics Committee with any additional requested information, notably for reported deaths of subjects.

7.5.1 Handling of Expedited Safety Reports

In accordance with local regulations, BMS and Dendreon will notify investigators of all SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the Investigator Brochure). Investigator notification of these events will be in the form of an expedited safety report (ESR).

Other important findings which may be reported by the sponsor as an ESR include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (e.g., animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.

Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the Investigator Brochure. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

7.5.2 Non-serious Adverse Events

The collection of non-serious AE information should begin at initiation of investigational product. If an ongoing non-serious AE worsens in its intensity, or if its relationship to the investigational product changes, a new non-serious AE entry for the event should be completed. Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of investigational product, or those that are present at the end of study participation. Subjects with non-serious AEs at study completion should receive post-treatment follow-up as appropriate.

All identified non-serious AEs must be recorded and described in the medical record.

7.5.3 Pregnancy

Study participants must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized. Before study enrollment, study participants and their partners must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. The study participant must sign an informed consent form documenting this discussion.

Any pregnancy that occurs in a female partner of a male study participant should be reported to the sponsors.

7.6 Data Safety Monitoring Plan

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology, blood chemistry and urine values, regular measurement of vital signs and the performance of physical examinations.

7.6.1 Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and subject safety for all HDFCCC institutional clinical studies. A summary of DSMC activities for this study include:

- Review of subject data
- Review of suspected adverse reactions considered "serious"
- Monitoring every six months (depending on study accrual)
- Minimum of a yearly regulatory audit

7.6.2 Monitoring and Reporting Guidelines

Investigators will conduct continuous review of data and subject safety and discuss each subject's treatment at monthly Site Committee meetings. These discussions are documented in the Site Committee meeting minutes. The discussion will include the number of subjects, significant toxicities in accordance with the protocol, and observed responses.

All institutional Phase 2 or 3 studies are designated with a moderate risk assessment. The data is monitored twice per year with twenty percent of the subjects monitored (or at least three subjects if the calculated value is less than three). The participating site(s) will submit the source documents electronically for the UCSF DSMC to perform remote monitoring and source document verification as per the attached Data and Safety Monitoring Plan for Multicenter Studies (Phase 2 or 3 Institutional Study) (Appendix 8).

7.6.3 Review and Oversight Requirements

7.6.3.1 Adverse Event Monitoring

All grade(s) 3-5 adverse events, whether or not unexpected, and whether or not considered to be associated with the use of the study drug, will be entered into OnCore®, UCSF's Clinical Trial Management System.

All grade(s) 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the Site Committee meetings. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s).

In addition, all suspected adverse reactions considered "serious" entered into OnCore®, will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or

to a study procedure, the Investigator or his/her designee must notify the DSMC Chair within 1 business day of knowledge of this event. The contact may be by phone or e-mail.

7.6.3.2 SAE Reporting

The principal investigator has the obligation to report all serious adverse events to the UCSF IRB, Bristol-Myers Squibb Company Global Pharmacovigilance and Epidemiology department, and Dendreon Pharmacovigilance (PV).

Bristol-Myers Squibb Company Global Pharmacovigilance and Epidemiology department

SAEs should be reported on the MedWatch form 3500A, which can be accessed at:
http://www.accessdata.fda.gov/scripts/medwatch/
MedWatch SAE forms should be sent to the FDA at:
MEDWATCH [redacted]
All SAEs should be simultaneously faxed or e-mailed to BMS at:
Global Pharmacovigilance & Epidemology Bristol-Myers Squibb Company [redacted]

All SAEs that occur from the 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 (Form is provided in Appendix 10). Sponsor shall notify institution, investigator and IRB immediately during the conduct of the study and/or after the study is completed should it become aware of information related to the study that would impact participant safety or clinical care. Institution shall promptly disclose such information to study participants.

Dendreon Corporation

Attn: Safety Manager

[redacted]

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

Any Serious Adverse Event (SAE) will be reported to the local institution's IRB and the UCSF GU Medical Oncology Clinical Research Program as specified below. Serious Adverse events will be reported on the MedWatch form. The date the SAE was sent to all required reporting agencies will be documented on OnCore, hard copies of the report will be maintained in the regulatory files. UCSF will circulate all SAE's to the participating centers.

Any adverse event falling under the definition of Serious will be reported immediately to the Study Chairman who, in turn, must notify the UCSF IRB per IRB policy. Symptoms related to

progressive disease such as severe bone pain will not be reported as toxicity or as Serious Adverse Events.

UCSF IRBwebsite for guidance in reporting serious adverse events:
http://www.research.ucsf.edu/chr/Guide/chrA_AE.asp

MedWatch forms and information: http://www.fda.gov/medwatch/getforms.htm

Multi-center sites participating in the study will notify the UCSF GU Medical Oncology Clinical Research Program [redacted] of all serious adverse events within 24 hours of knowledge of the event. The UCSF clinical research staff will immediately notify the principal investigator (PI) or his designee of the SAE. The participating institutions will submit the SAE to their own IRB. The participating institution must forward a copy of the report filed with their local IRB to the UCSF Urologic Oncology Clinical Research Program within 5 calendar days. After the UCSF clinical research staff receives and processes the initial SAE report from the participating institution, it will be forwarded to the PI or his designee for review and signature. If the SAE is death, and is determined to be possibly, probably or definitely related to the investigational drug or any research related procedure, the event must be reported to the DSMC Chair or his designee within 24 business hours. The reporting procedure is by personal communication via phone or in person with written documentation of the one-on-one communication via e-mail with a copy of the e-mail to the DSMC Administrator.

7.6.4 Review of Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, a report should be submitted to the DSMC at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Investigator stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Manager must be notified within 1 business day via e-mail. The DSMC must receive a formal letter within 10 business days and the CHR must be notified.

Data and Safety Monitoring Committee Contacts:

DSMC Chair:
Phone:
Email:
Address: [redacted]
UCSF
San Francisco, CA 94115

DSMC Monitors
[redacted]
UCSF Helen Diller Family
Comprehensive Cancer Center
San Francisco, CA 94115

8 INVESTIGATIONAL PRODUCTS

The investigational product is defined as a pharmaceutical form of an active ingredient being tested as a reference in the study, whether blinded or open-label. In this study, the investigational product is ipilimumab.

8.1 Identification

Ipilimumab is available in concentrations of 5 mg/mL (50 mg/10 mL and 200 mg/40 mL). The sterile solution in the vial is clear and colorless. Ipilimumab is administered via intravenous infusion only.

8.2 Packaging and Labeling

BMS will provide ipilimumab at no cost for this study. Ipilimumab will be provided in open-label containers. The labels will contain the protocol prefix, batch number, content, storage conditions, and dispensing instructions along with the Investigational New Drug (IND) caution statement.

8.3 Storage, Handling, and Dispensing

8.3.1 Storage

Ipilimumab must be stored in a secure area according to local regulations. The investigator must ensure that it is stored at a temperature ≥ 2°C and ≤ 8°C.

8.3.2 Handling and Disposal

As with all injectable drugs, care should be taken when handling and preparing ipilimumab. Whenever possible, ipilimumab should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents applying aseptic technique. Latex gloves are required. If ipilimumab concentrate or solution comes in contact with skin or mucosa, immediately and thoroughly wash with soap and water. After final drug reconciliation, unused ipilimumab solution should be disposed at the site following procedures for the disposal of anticancer drugs.

8.3.3 Dispensing

It is the responsibility of the investigator to ensure that ipilimumab is only dispensed to study subjects. The ipilimumab must be dispensed only from official study sites by authorized personnel according to local regulations.

8.4 Drug Ordering and Accountability

8.4.1 Initial Orders

Following submission and approval of the required regulatory documents, a supply of ipilimumab may be ordered from BMS. Investigators must complete a Drug Request Form and email it to: distribution.allentown@thermofisher.com.

If for any reason the e-mail drug request form is not successfully transmitted, contact [redacted] Fisher Clinical Services:

[redacted] www.fisherclinicalservices.com

It is recommended you send a test message to the Fisher Clinical Service e-mail address upon receipt of the Drug Request Form. Please include in the subject line: "BMS IST Drug Order -- Test." This will ensure your site is recognized by Fisher and your future orders will be received without incident.

Ipilimumab vials (40 mL) are shipped in quantities of five. The initial order should be limited to 25 vials (5 cartons of 5 vials each). Allow 5 business days for shipment of drug from BMS receipt of the Drug Request Form. Drug is protocol specific, but not patient specific. All product will be shipped via Federal Express in a temperature-controlled container. Shipments will be made from Fisher Clinical Services on Monday through Thursday for delivery onsite Tuesday through Friday. There will be no weekend or holiday delivery of drugs.

It is possible that sites may have more than one ipilimumab clinical study ongoing at the same time. **It is imperative that only product designated for this protocol number be used for this study.** To help segregate product for this study from other investigational or marketed product, stickers bearing the BMS protocol number will be provided and should be affixed to the front of the outer carton just above the company names so as not to obscure any marking.

8.4.2 Re-Supply

Reorders should be emailed directly to Fisher Clinical Services [redacted] for shipment within 5 business days. When assessing need for resupply, institutions should keep in mind the number of vials used per treatment dose, and that shipments may take 5 business days from BMS receipt of request. Drug is not patient specific. Be sure to check with your pharmacy regarding existing investigational stock to assure optimal use of drug on hand.

8.5 Ipilimumab Accountability

It is the responsibility of the investigator to ensure that a current record of ipilimumab disposition is maintained at each study site where ipilimumab is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area.
- Amount currently in storage area.
- Label ID number or batch number and use date or expiry date.
- Dates and initials of person responsible for each ipilimumab inventory entry/movement.
- Amount dispensed to and returned by each subject, including unique subject identifiers.
- Amount transferred to another area/site for dispensing or storage.
- Non-study disposition (e.g., lost, wasted, broken).
- Amount destroyed at study site.

8.6 Ipilimumab Destruction

If ipilimumab is to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for disposal and that procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures. Appropriate records of the disposal must be maintained.

9 STATISTICAL METHODOLOGY

9.1 Sample Size Considerations

9.1.1 Safety Lead-in

Six patients at the 3 mg/kg dose of ipilimumab will be randomized to Arm 1 and 2, immediate versus delayed ipilimumab after 4 doses of SipT. If DLTs are encountered as defined above (Section 3.1), then one or both arms may be discontinued. 6 patients will be required to complete this phase of the study.

9.1.2 Phase 2

Primary Immune Objective: This is a multicenter non-comparative randomized Phase 2 trial with the primary objective of immunologic efficacy in addition to safety. Immune response is defined as an IgG antibody response to either PAP or PA2024 by study week 20. The IgG antibody response will be determined with an ELISA assay with a positive response defined as titer > 1:400. To achieve a 40% immune response rate indicating immune activity versus a null hypothesis of 15% indicating lack of immune activity assuming a 2-sided type I error of 5% and 81% power will require 27 total patients per arm. This is based upon the exact binomial test for a single sample. The null hypothesis of 15% is based off an observed anti-PAP IgG response rate of 17.7% seen at a similar time interval in patients treated with sipuleucel-T in the three phase 3 clinical trials[46]. Therefore, an additional 21 patients beyond the safety lead-in phase will be accrued to each arm (an additional 42 patients). The total number of evaluable patients for the Phase 2 study will be 54 patients with accrual up to 66 patients possible. Patients will be accrued at UCSF and MDACC with the randomization to ipilimumab timing stratified by institution.

Secondary Immune Objectives: The sample size with 27 patients in each arm is sufficient to detect a mean difference between the two study arms in immune modulation, a secondary objective, for an effect size (standardized unit) of at least 0.69 for normally distributed variables. Similarly, the sample size is sufficient to detect at least a 37% difference between the two treatment groups in proportions of patients displaying a specific outcome using Fisher's exact test (e.g. 33% versus 70% achieving a certain change in an immune parameter). For both types of tests a level of significance of 0.05 for a directional test and power of at least 0.80 is assumed. Directional tests will be performed to test for an effect due to the timing of ipilimumab. A directional test is being used because a greater immune effect is expected with immediate administration of ipilimumab.

9.2 Stopping Rules

9.2.1 Stopping Rules for Efficacy

There will be no interim analysis for efficacy due to the small sample size of each treatment arm. Although a secondary outcome measure is PSA decline, additional exploratory analyses will be performed to investigate the relationship between evidence of immune activation and clinical response to aid in designing future investigations.

9.2.2 Stopping Rules for Toxicity

A stopping rule for safety will be applied separately to each arm for the Phase 2 study. Six patients on each arm from the safety lead-in study are included in the phase II study and will have already been evaluated for safety. Within each arm, we will stop accrual if there are 3 SigAEs among the next 10 randomized patients (total accrual per arm would be 16 patients). Following these 10 patients, safety would then be assessed cumulatively and accrual will continue unless 20% or more of all treated patients on a single arm experience a SigAE as defined in section 7.3.2. If this frequency of SigAEs is observed in one arm but not in the other, then the arm with the SigAEs will be discontinued while the arm without sigAEs will continue.

9.3 Methods for Analysis

9.3.1 Primary Endpoints

9.3.1.1 Safety Lead-in: Assess the safety of combining ipilimumab with SipT.

Toxicities will be reported for each study arm at each dose of ipilimumab administered with descriptive statistics (e.g. proportions) by tabulating the frequency of the maximum grade occurring for each patient for each type using NCI CTC v. 4.0 criteria. As described above the type and grade of all such IRAEs will be tabulated by treatment arm. Toxicity results will be presented indicating occurrences during the first 20 weeks of protocol therapy and those occurring later.

9.3.1.2 Phase 2: Determine whether the timing of ipilimumab administration impacts PAP and PA2024 specific immune responses by SipT

The primary immune study hypothesis to assess the frequency of observing an immune response to PAP and/or PA2024 by week **20**, when the induction ipilimumab therapy is completed, for each of the two ipilimumab schedules will be tested using the single sample binomial exact test. The IgM and IgG antibody responses to PAP and PA2024 will be assessed with an ELISA assay at baseline and week 20 after the start of sipT treatment (day 113 of study treatment). A positive response will be defined as a titer > 1:400. The primary hypothesis will be tested by comparing the proportion of patients achieving an IgG immune response to PAP or PA2024 to the null hypothesis of 15% (based off an observed anti-PAP IgG response rate of 17.7% seen at a similar time interval in patients treated with sipuleucel-T in the three phase 3 clinical trials[46]. using a single sample exact test for binary variables as defined above in the sample size justification. The same single sample test will be performed for IgM antibodies. The positive immune proportion for both IgG and IgM antibodies to PAP and to PA2024 with 95% confidence intervals will be used to summarize the results for each study arm. No adjustment for multiple comparisons will be made.

Exploratory analyses investigating the change in antibody response from baseline to week 20 when response is considered as a binary variable (positive or negative) will be investigated using the Mantel-Haenszel chi square statistic stratified by treatment arm. When the ELISA results are treated as continuous variables the change in each immune response will be analyzed using analysis of variance (ANOVA) methods.

9.3.2 Secondary Endpoints

9.3.2.1 PSA Decline

Descriptive statistics will be used to characterize the disease and treatment factors for patients accrued to each study arm. The two treatment arms will be compared for comparability of baseline disease features and immune parameters using a chi square test for categorical variables, a t test for normally distributed continuous variables and the nonparametric Mann-Whitney test when the normality assumption cannot be assumed.

Descriptive statistics will be calculated to characterize the proportion of patients achieving a PSA decline of at least >30% and >50% and presented along with the 95% confidence intervals for each study arm. The maximum overall change in PSA will be summarized by waterfall plots for each study arm. Similarly, the proportion of patients achieving an objective response will also be determined. Descriptive statistics will be presented for each study arm to summarize response according to important disease features such as LDH (abnormal vs. normal) and prior treatment (radiation therapy, RP, systemic steroid usage > 3 months). Descriptive statistics will be used to summarize time to PSA progression. The Kaplan-Meier product limit will be used to estimate the probability of time to PSA progression with durations measured from the start of protocol therapy. For each study arm the median time to progression with 95% confidence intervals will be presented to summarize clinical efficacy.

9.3.2.2 Radiographic Clinical Responses

For each treatment arm, for patients with objective disease, using immune-related response criteria (irRC) criteria, the proportion of patients achieving a complete or partial response will be determined and reported with 95% confidence intervals.

9.3.2.3 Modulation of Effector and Regulatory T Cells

The secondary outcome measures of T cell immune activation will be compared between the two treatment arms. Exploratory analyses of antigen-specific T cell responses to PAP and PA2024 will be measured at weeks 0, 4(study day 1), 7(day 22), 10(day 43), 13 (day 64), 16 (day 85), 20 (day 113), 32 (day 197) with IFNg ELISPOT. Samples will be obtained just prior to treatment. A T cell response to each of the antigens will be defined as $\geq$10 spots/300,000. For each antigen (PAP and PA2024), the proportion of positive responses by treatment arm at week 20 will be calculated and presented with 95% confidence intervals. Agreement in antibody and T cell responses will be explored at each time point with McNemar's test for paired binary data. In addition, a test of when a T cell immune response is first recognized will also be identified using ANOVA methods when the T cell response is evaluated as a continuous variable. There will not be any adjustment for multiple comparisons for these exploratory analyses.

Exploratory ANOVA analyses for mixed models will also be used to compare the magnitude or the change from baseline in activated CD4 and CD8 T cells to week 7, 10, 13, 16, and 20 of treatment between the two treatment arms. Activation markers to be assessed on CD4 and CD8 T cells by flow cytometry will include ICOS/ICOS-L; OX40/OX40-L; 41BB/41BB-L; PD-1/PD-L1 and PD-L2; CD69, and HLA-DR. Similar comparisons of the magnitude or change from baseline in FoxP3+ CD4+ Regulatory T cells at these same time points will be evaluated.

Additional exploratory analyses again using ANOVA methods will be performed to determine whether there is a difference in baseline levels or change by week 14 and 20 in T cell activation markers between those achieving a PSA decline of at least 30% or not.

10 ADMINISTRATIVE SECTION

10.1 Multicenter Communication

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center for Phase II studies will also coordinate, at minimum, monthly conference calls with the participating sites at the completion of each cohort or more frequently as needed to discuss risk assessment. The following issues will be discussed as appropriate:

- Enrollment information
- Adverse events (i.e. new adverse events and updates on unresolved adverse events and new safety information)
- Protocol violations
- Other issues affecting the conduct of the study
- Record Keeping and Record Retention

The Principal Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

Prior to implementing this protocol at UCSF HDFCCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the UCSF Committee on Human Research (IRB). Prior to implementing this protocol at the participating sites, approval for the UCSF IRB approved protocol must be obtained from the participating site’s IRB.

The following documents must be provided to UCSF HDFCCC before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved consent form
- Participating Site IRB membership list
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site
- Participating site laboratory certifications and normals

UCSF will also request that all sub-sites send their Data Safety and Monitoring Plan (DSMP) to UCSF for review for approval. If a sub-site does not have its own DSMP in place, UCSF will at that time review the resources necessary to include that sub-site and determine whether the UCSF study personnel are able to manage the regulatory burden for that sub-site. Upon receipt of the required documents, UCSF HDFCCC will formally contact the site and grant permission to proceed with enrollment.

10.2 Coordinating Center Documentation of Distribution

It is the responsibility of the Study Chair to maintain adequate files documenting the distribution of study documents as well as their receipt (when possible). The HDFCCC recommends that the Study Chair maintain a correspondence file and log for each segment of distribution (e.g., FDA, drug manufacturer, participating sites, etc.).

Correspondence file: should contain copies (paper or electronic) of all protocol versions, cover letters, amendment outlines (summary of changes), etc., along with distribution documentation and (when available) documentation of receipt.

Correspondence log: should be a brief list of all documents distributed including the date sent, recipient(s), and (if available) a tracking number and date received.

At a minimum, the Study Chair must keep documentation of when and to whom the protocol, its updates and safety information are distributed.

10.3 Registration

A centralized, 3-part registration procedure will be used. After eligibility screening, patients selected to participate will be registered with their study site/institution first, then with the lead center and finally in the consortium database (OnCore).

Institutional Registration

Patient registration at each study site/institution will be conducted according to the institution's established policies. Prior to registration, patients will be asked to sign and date an Institutional Review Board (IRB)-approved consent form and a research authorization form/Heath Insurance Portability and Accountability Act (HIPAA) authorization form. Patients must be registered with the institution before beginning any treatment or study activities.

Lead Center Registration

To initiate lead center registration, study sites/institutions should forward copies of the signed informed consent, research authorization/ and HIPAA forms, and the completed and signed eligibility checklist to the lead center research coordinator [redacted]. Upon receipt of these forms, the lead center will assign a unique patient study identification number, and send a confirmation of patient registration to the local coordinator via electronic mail. A copy of this confirmation will be retained by both the lead and local centers.

A patient cannot be treated until confirmation of enrollment is received.

Consortium Registration

Once registration has been completed at the patient's institution and with the Lead Center, the patient will be registered in the centralized database for the consortium (OnCore).

10.4 Case Report Forms (CRFs)

The Principal Investigator and/or his/her designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. Site personnel will complete the CRFs as soon as possible upon completion of the study visit; the Investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents.

In accordance with federal regulations, the site investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs.

All source documentation and CTMS data will be available for review/monitoring by the UCSF DSMC and regulatory agencies.

10.5 Changes in the Protocol

Once the protocol has been approved by the local IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the Investigator and approved by the local IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to IRB approval. In this circumstance, however, the Investigator must then notify the IRB in writing within five (5) working days after implementation. The Study Chair and the UCSF study team will be responsible for updating any participating sites.

10.6 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the site IRB-approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

10.7 Record Keeping and Record Retention

The Principal Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data (e.g., signed and dated consent forms and medical records, such as progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Study Chair correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the site investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

10.8 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s). This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

Systems with procedures that ensure the quality of every aspect of the study will be implemented.

10.9 Protection of Human Subjects

Protection from Unnecessary Harm

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the IRB mechanism and the process of informed consent. The IRB reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

Protection of Privacy

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

10.10 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, each site Investigator will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

The clinical investigation will not begin until the FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed.

Each site investigator must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory requirements. The local IRBs must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

10.11 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g., advertisements used to recruit participants) will be reviewed and approved by each site's local Institutional Review Board. The initial protocol and all protocol amendments must be approved by each site's local IRB prior to implementation.

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APPENDIX 1: LIST OF ABBREVIATIONS

Abbreviation	Term
ANC	Absolute Neutrophil Count
BID	Twice a Day
BMS	Bristol-Myers Squibb Company
CT scan	Computed Axial Tomography scan
CBC	Complete Blood Count
CR	Complete Response
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
ECOG PS	Eastern Cooperative Oncology Group Performance Status
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
irRC	Immune related response criteria
MRI	Magnetic Resonance Imaging
PD	Progressive Disease
PFS	Progression Free Survival
PO	By Mouth
PR	Partial Response
QD	Once Daily
QoL	Quality Of Life
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SipT	Sipuleucel-T
SPD	Sum of the products diameters
SD	Stable Disease
TNM Staging	Tumor, Node and Metastasis Staging
TA	Tumor assessment

APPENDIX 2: CLINICAL MONITORING FOR AUTOIMMUNITY

(To be completed at each MD visit)

Patient ID _____

Day # _____

Hepatic

Symptoms _____

Signs _____

Labs

_____ AST/ALT

_____ Bilirubin (total)

_____ ALP

Gastrointestinal

Symptoms _____

Signs _____

_____ No diarrhea

_____ increase of < 4 stools/day

_____ increase of 4-6 stools/day

_____ increase of ≥ 7 stools/day, or need for parenteral support

_____ diarrhea requiring ICU admission or hemodynamic compromise

_____ nausea/vomiting

Labs

_____ Stool analysis (include WBC count) for patients with GI symptoms

Pancreas

Symptoms _____

Signs _____

Labs

_____ amalyase

_____ lipase

_____ glucose

UCSF MRN_____

Date_____

Skin

Symptoms _____

Signs (include pruritis, vitiligo) _____

_____

_____ no rash

_____ rash; description _____

_____

_____ % of body surface

Pulmonary

Symptoms _____

Signs _____

Rheumatologic

Symptoms _____

Signs (include joint pain swelling; #/location of joints involved) _____

_____

Labs

_____ ANA (titer, pattern)

_____ RF

Other _____

Renal

Symptoms _____

Signs _____

Labs

_____ Cr

Endocrine

Symptoms _____

Signs _____

Labs

_____ TSH

_____ T4

_____ FTI

Pituitary

_____

_____

Neurologic

Symptoms _____

Signs _____

Hematologic

Symptoms _____

Signs _____

Labs

_____ WBC

_____ Hgb

_____ Plt

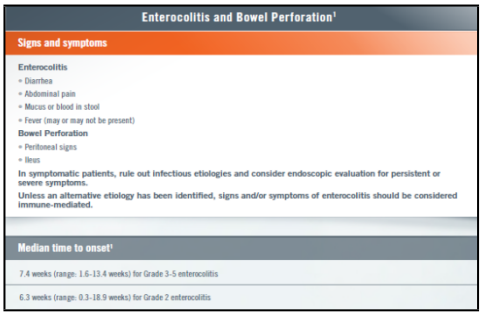
_____ ANC

Cardiac

Symptoms _____

Signs _____

APPENDIX 3: GI TOXICITY MANAGEMENT ALGORITHM



Enterocolitis and Bowel Perforation[1]

Signs and symptoms

Enterocolitis
- Diarrhea
- Abdominal pain
- Mucus or blood in stool
- Fever (may or may not be present)

Bowel Perforation
- Peritoneal signs
- Ileus

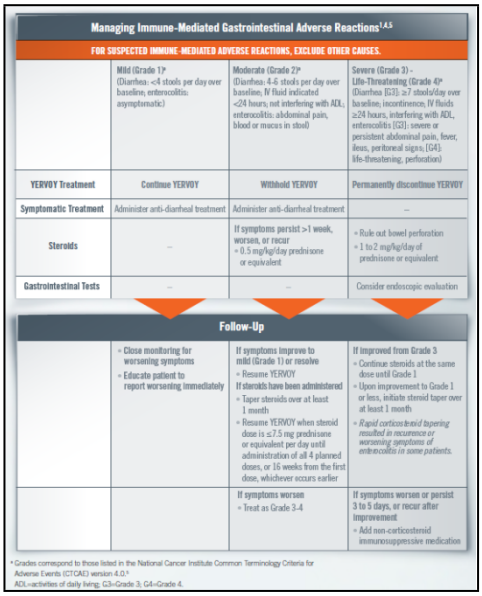
In symptomatic patients, rule out infectious etiologies and consider endoscopic evaluation for persistent or severe symptoms.

Unless an alternative etiology has been identified, signs and/or symptoms of enterocolitis should be considered immune-mediated.

Median time to onset[1]

7.4 weeks (range: 1.6–13.4 weeks) for Grade 3–5 enterocolitis

6.3 weeks (range: 0.3–18.9 weeks) for Grade 2 enterocolitis



Managing Immune-Mediated Gastrointestinal Adverse Reactions[1,4,5]

FOR SUSPECTED IMMUNE-MEDICATED ADVERSE REACTIONS, EXCLUDE OTHER CAUSES.

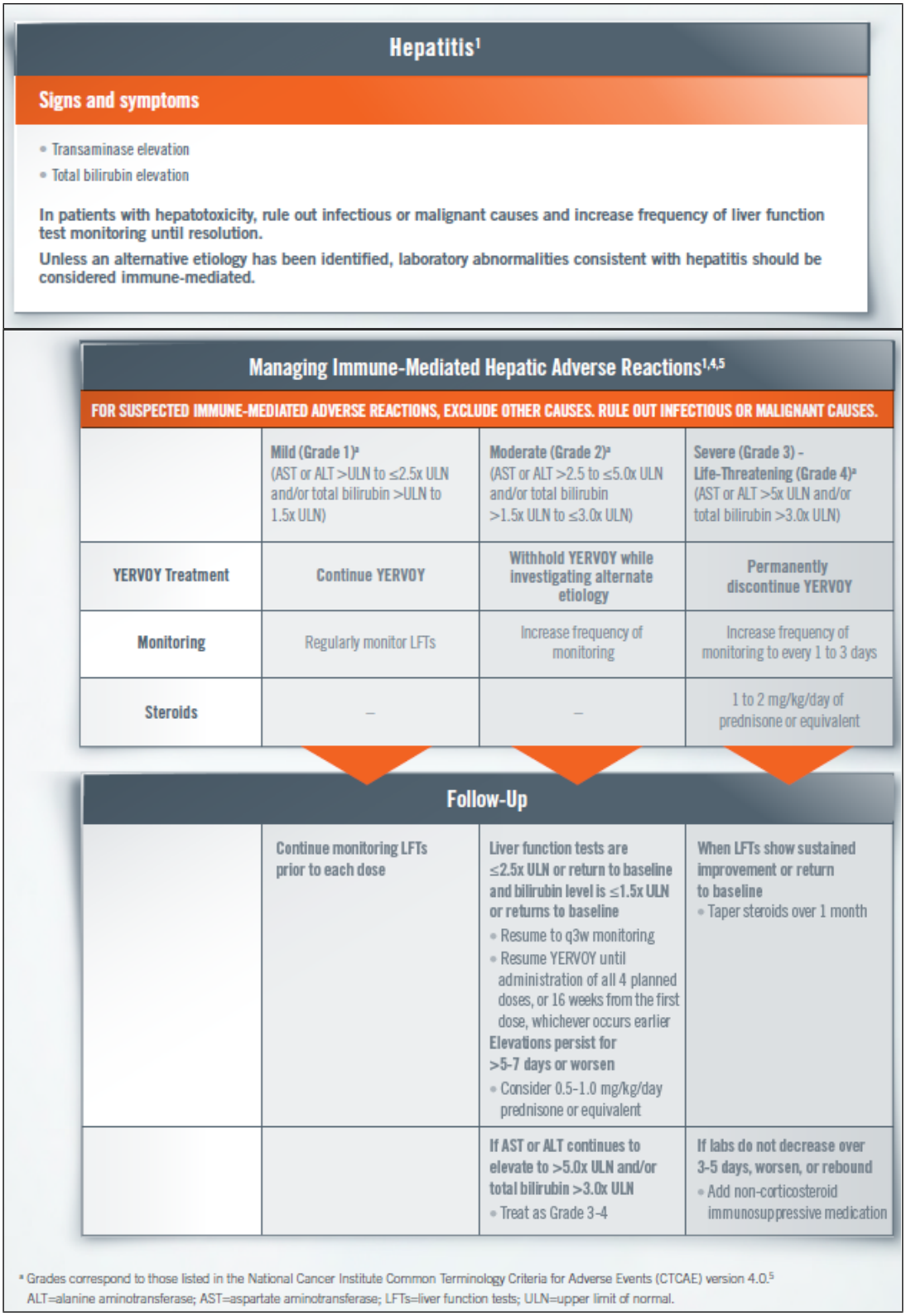
	Mild (Grade 1)* (Diarrhea: <4 stools per day over baseline; enterocolitis: asymptomatic)	Moderate (Grade 2)* (Diarrhea: 4-6 stools per day over baseline; IV fluid indicated <24 hours; not interfering with ADL; enterocolitis: abdominal pain, blood or mucus in stool)	Severe (Grade 3) - Life-Threatening (Grade 4)* (Diarrhea [G3]: ≥7 stools/day over baseline; incontinence; IV fluids ≥24 hours; interfering with ADL; enterocolitis [G3]: severe or persistent abdominal pain, fever, ileus, peritoneal signs; [G4]: life-threatening, perforation)
YERVOY Treatment	**Continue YERVOY**	**Withhold YERVOY**	**Permanently discontinue YERVOY**
Symptomatic Treatment	Administer anti-diarrheal treatment	Administer anti-diarrheal treatment	–
Steroids	–	If symptoms persist >1 week, worsen, or recur • 0.5 mg/kg/day prednisone or equivalent	• Rule out bowel perforation • 1 to 2 mg/kg/day of prednisone or equivalent
Gastrointestinal Tests	–	–	Consider endoscopic evaluation

Follow-Up

	• Close monitoring for worsening symptoms • Educate patient to report worsening immediately	If symptoms improve to mild (Grade 1) or resolve • Resume YERVOY If steroids have been administered • Taper steroids over at least 1 month • Resume YERVOY when steroid dose is ≤7.5 mg prednisone or equivalent per day until administration of all 4 planned doses, or 16 weeks from the first dose, whichever occurs earlier	If improved from Grade 3 • Continue steroids at the same dose until Grade 1 • Upon improvement to Grade 1 or less, initiate steroid taper over at least 1 month • *Rapid corticosteroid tapering resulted in recurrence or worsening symptoms of enterocolitis in some patients.*
		If symptoms worsen • Treat as Grade 3-4	If symptoms worsen or persist 3 to 5 days, or recur after improvement • Add non-corticosteroid immunosuppressive medication

*Grades correspond to those listed in the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.[6]
ADL=activities of daily living; G3=Grade 3; G4=Grade 4.

APPENDIX 4: HEPATOTOXICITY MANAGEMENT ALGORITHM



Hepatitis[1]

Signs and symptoms

- Transaminase elevation
- Total bilirubin elevation

In patients with hepatotoxicity, rule out infectious or malignant causes and increase frequency of liver function test monitoring until resolution.

Unless an alternative etiology has been identified, laboratory abnormalities consistent with hepatitis should be considered immune-mediated.

Managing Immune-Mediated Hepatic Adverse Reactions[1,4,5]

FOR SUSPECTED IMMUNE-MEDIATED ADVERSE REACTIONS, EXCLUDE OTHER CAUSES. RULE OUT INFECTIOUS OR MALIGNANT CAUSES.

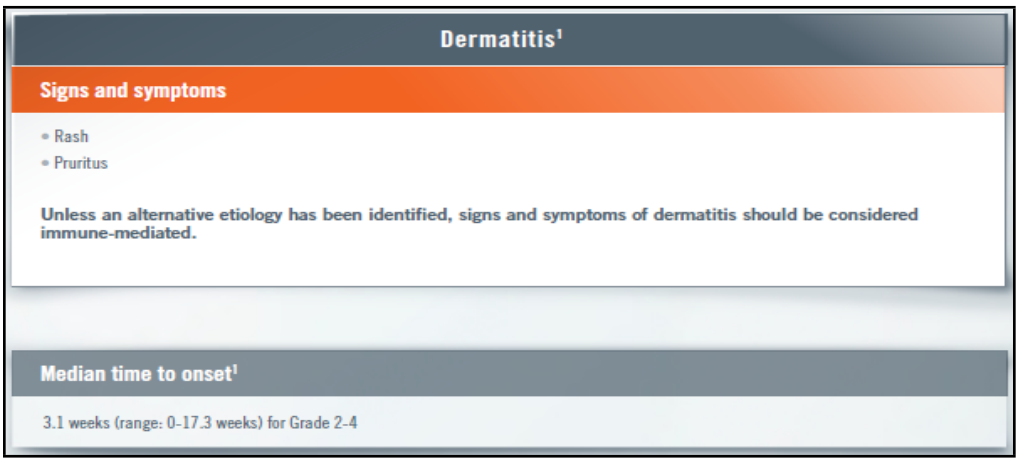
	Mild (Grade 1)[a] (AST or ALT >ULN to ≤2.5x ULN and/or total bilirubin >ULN to 1.5x ULN)	Moderate (Grade 2)[a] (AST or ALT >2.5 to ≤5.0x ULN and/or total bilirubin >1.5x ULN to ≤3.0x ULN)	Severe (Grade 3) - Life-Threatening (Grade 4)[a] (AST or ALT >5x ULN and/or total bilirubin >3.0x ULN)
YERVOY Treatment	**Continue YERVOY**	**Withhold YERVOY while investigating alternate etiology**	**Permanently discontinue YERVOY**
Monitoring	Regularly monitor LFTs	Increase frequency of monitoring	Increase frequency of monitoring to every 1 to 3 days
Steroids	–	–	1 to 2 mg/kg/day of prednisone or equivalent

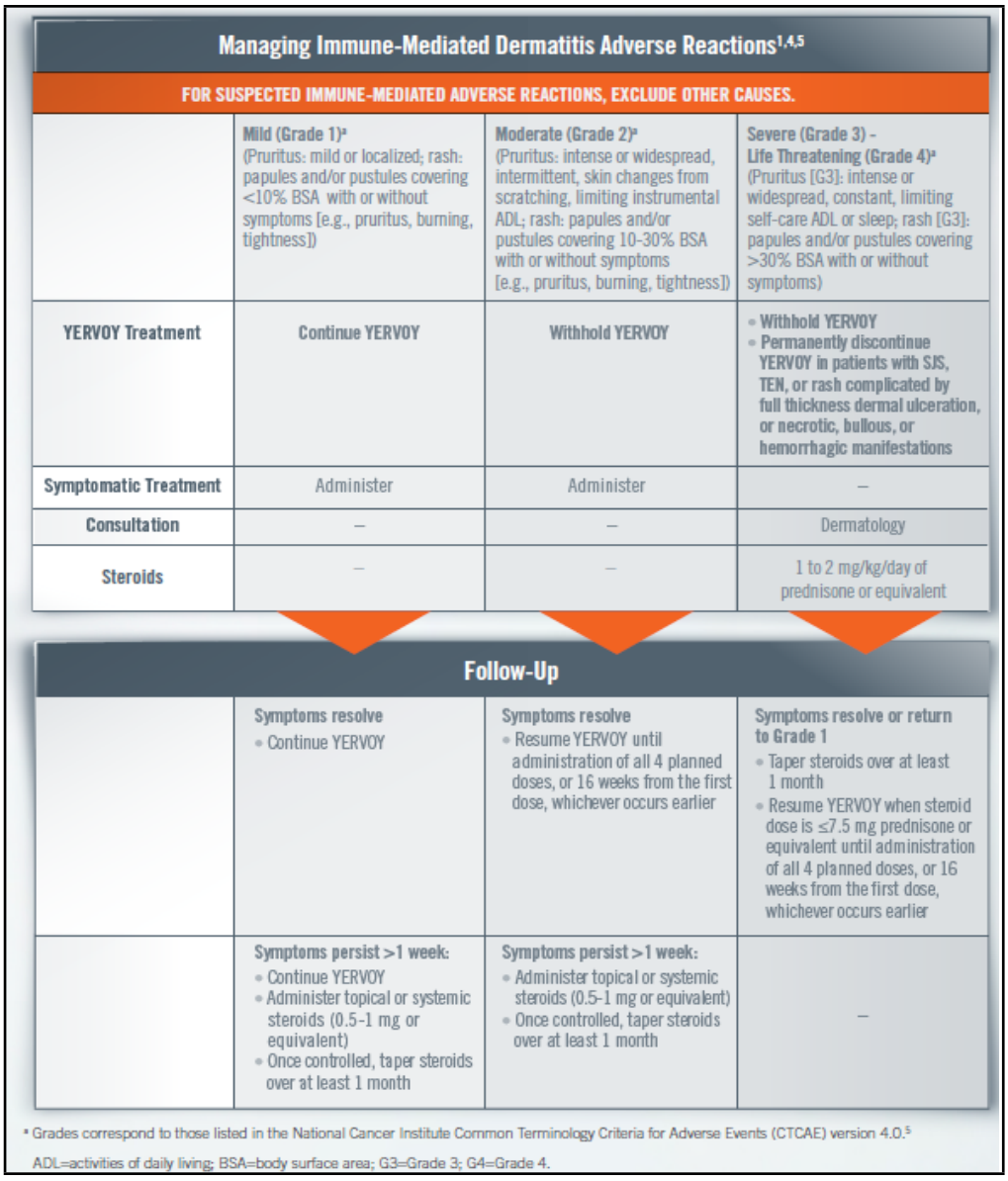
Follow-Up

	Continue monitoring LFTs prior to each dose	**Liver function tests are ≤2.5x ULN or return to baseline and bilirubin level is ≤1.5x ULN or returns to baseline** • Resume to q3w monitoring • Resume YERVOY until administration of all 4 planned doses, or 16 weeks from the first dose, whichever occurs earlier **Elevations persist for >5-7 days or worsen** • Consider 0.5-1.0 mg/kg/day prednisone or equivalent	**When LFTs show sustained improvement or return to baseline** • Taper steroids over 1 month
		If AST or ALT continues to elevate to >5.0x ULN and/or total bilirubin >3.0x ULN • Treat as Grade 3-4	**If labs do not decrease over 3-5 days, worsen, or rebound** • Add non-corticosteroid immunosuppressive medication

[a] Grades correspond to those listed in the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.[5]
ALT=alanine aminotransferase; AST=aspartate aminotransferase; LFTs=liver function tests; ULN=upper limit of normal.

APPENDIX 5: SKIN TOXICITY MANAGEMENT ALGORITHM





Managing Immune-Mediated Dermatitis Adverse Reactions[1,4,5]

FOR SUSPECTED IMMUNE-MEDIATED ADVERSE REACTIONS, EXCLUDE OTHER CAUSES.

	Mild (Grade 1)[a] (Pruritus: mild or localized; rash: papules and/or pustules covering <10% BSA with or without symptoms [e.g., pruritus, burning, tightness])	Moderate (Grade 2)[a] (Pruritus: intense or widespread, intermittent, skin changes from scratching, limiting instrumental ADL; rash: papules and/or pustules covering 10-30% BSA with or without symptoms [e.g., pruritus, burning, tightness])	Severe (Grade 3) - Life Threatening (Grade 4)[a] (Pruritus [G3]: intense or widespread, constant, limiting self-care ADL or sleep; rash [G3]: papules and/or pustules covering >30% BSA with or without symptoms)
YERVOY Treatment	**Continue YERVOY**	**Withhold YERVOY**	• **Withhold YERVOY** • **Permanently discontinue YERVOY in patients with SJS, TEN, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations**
Symptomatic Treatment	Administer	Administer	–
Consultation	–	–	Dermatology
Steroids	–	–	1 to 2 mg/kg/day of prednisone or equivalent

Follow-Up

	Symptoms resolve • Continue YERVOY	**Symptoms resolve** • Resume YERVOY until administration of all 4 planned doses, or 16 weeks from the first dose, whichever occurs earlier	**Symptoms resolve or return to Grade 1** • Taper steroids over at least 1 month • Resume YERVOY when steroid dose is ≤7.5 mg prednisone or equivalent until administration of all 4 planned doses, or 16 weeks from the first dose, whichever occurs earlier
	Symptoms persist >1 week: • Continue YERVOY • Administer topical or systemic steroids (0.5-1 mg or equivalent) • Once controlled, taper steroids over at least 1 month	**Symptoms persist >1 week:** • Administer topical or systemic steroids (0.5-1 mg or equivalent) • Once controlled, taper steroids over at least 1 month	–

[a] Grades correspond to those listed in the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.[5]

ADL=activities of daily living; BSA=body surface area; G3=Grade 3; G4=Grade 4.

APPENDIX 6: ENDOCRINOPATHY MANAGEMENT ALGORITHM

Endocrinopathies[1]

Signs and symptoms

- Fatigue
- Headache
- Mental status changes
- Abdominal pain
- Unusual bowel habits
- Hypotension

Patients may present with nonspecific symptoms that may resemble other causes, such as brain metastases or underlying disease.

Unless an alternative etiology has been identified, signs and/or symptoms of endocrinopathies should be considered immune-mediated.

Managing Immune-Mediated Endocrinopathies[1,4]

FOR SUSPECTED IMMUNE-MEDIATED ADVERSE REACTIONS, EXCLUDE OTHER CAUSES. CONSIDER VISUAL FIELD TESTING, ENDOCRINOLOGY CONSULTATION, AND IMAGING.

	Asymptomatic Endocrinopathy	Symptomatic Endocrinopathy	Suspicion of Adrenal Crisis (e.g., severe dehydration, hypotension, shock out of proportion to current illness)
YERVOY Treatment	**Continue YERVOY**	**Withhold YERVOY**	**Discontinue YERVOY**
Monitoring	If TSH <0.5x LLN, or TSH >2x ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycle as clinically indicated	• Evaluate endocrine function • Consider pituitary scan for hypophysitis • Repeat labs in 1 to 3 weeks/MRI in 1 month if symptoms persist but normal lab/pituitary scan	Rule out sepsis
Consultation	Consider Endocrinology	Consider Endocrinology	Endocrinology
Steroids	–	1-2 mg/kg/day prednisone or equivalent, if symptomatic with abnormal lab/pituitary scan	Stress-dose of IV steroids with mineralocorticoid activity[a]
Hormone Replacement	–	• Initiate if symptomatic with abnormal lab/pituitary scan • Long-term hormone replacement therapy may be necessary	–
IV Fluids	–	–	Administer

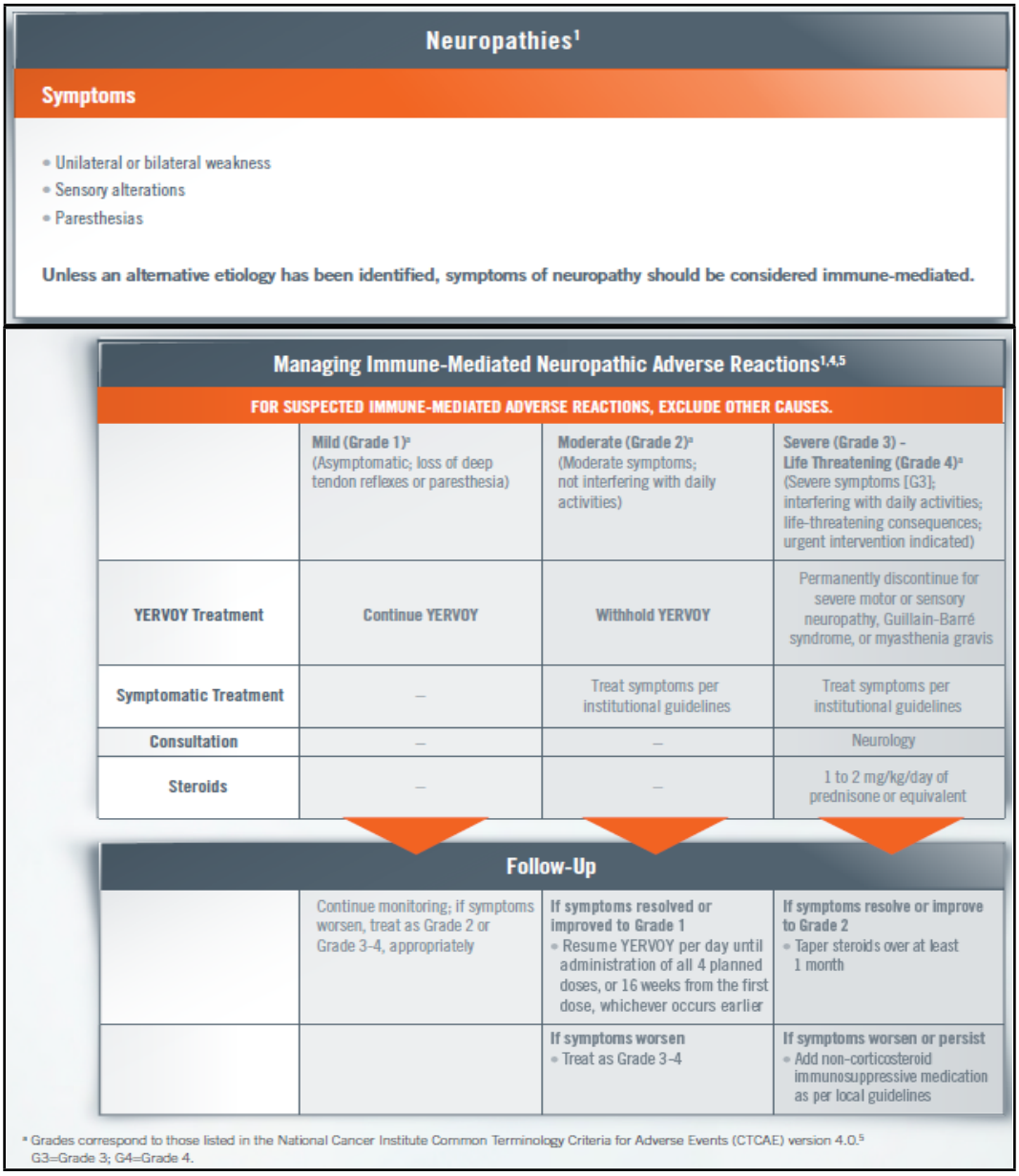
Follow-Up

	Continue standard monitoring	**If improved (with or without hormone therapy)** • Resume YERVOY when steroid dose is ≤7.5 mg prednisone or equivalent until administration of all 4 planned doses, or 16 weeks from the first dose, whichever occurs earlier • Taper steroids over at least 1 month **Continue standard monitoring** • Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component[a]	**When adrenal crisis ruled out** • Treat as *Symptomatic Endocrinopathy*

[a] Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to an equivalent dose of oral corticosteroids.

LLN=lower limit of normal; MRI=magnetic resonance imaging; T4=thyroxine; TSH=thyroid-stimulating hormone; ULN=upper limit of normal.

APPENDIX 7: NEUROLOGICAL TOXICITY MANAGEMENT ALGORITHM



Neuropathies[1]

Symptoms

- Unilateral or bilateral weakness
- Sensory alterations
- Paresthesias

Unless an alternative etiology has been identified, symptoms of neuropathy should be considered immune-mediated.

Managing Immune-Mediated Neuropathic Adverse Reactions[1,4,5]

FOR SUSPECTED IMMUNE-MEDIATED ADVERSE REACTIONS, EXCLUDE OTHER CAUSES.

	Mild (Grade 1)[a] (Asymptomatic; loss of deep tendon reflexes or paresthesia)	Moderate (Grade 2)[a] (Moderate symptoms; not interfering with daily activities)	Severe (Grade 3) - Life Threatening (Grade 4)[a] (Severe symptoms [G3]; interfering with daily activities; life-threatening consequences; urgent intervention indicated)
YERVOY Treatment	**Continue YERVOY**	**Withhold YERVOY**	Permanently discontinue for severe motor or sensory neuropathy, Guillain-Barré syndrome, or myasthenia gravis
Symptomatic Treatment	–	Treat symptoms per institutional guidelines	Treat symptoms per institutional guidelines
Consultation	–	–	Neurology
Steroids	–	–	1 to 2 mg/kg/day of prednisone or equivalent

Follow-Up

	Continue monitoring; if symptoms worsen, treat as Grade 2 or Grade 3-4, appropriately	**If symptoms resolved or improved to Grade 1** • Resume YERVOY per day until administration of all 4 planned doses, or 16 weeks from the first dose, whichever occurs earlier	**If symptoms resolve or improve to Grade 2** • Taper steroids over at least 1 month
		If symptoms worsen • Treat as Grade 3-4	**If symptoms worsen or persist** • Add non-corticosteroid immunosuppressive medication as per local guidelines

[a] Grades correspond to those listed in the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.[5] G3=Grade 3; G4=Grade 4.

Management of Other Immune-Mediated Adverse Reactions, Including Ocular Manifestations

- Permanently discontinue YERVOY for clinically significant or severe immune-mediated adverse reactions. Initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent for severe immune-mediated adverse reactions
- Administer corticosteroid eye drops to patients who develop uveitis, iritis, or episcleritis. Permanently discontinue YERVOY for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy

APPENDIX 8: TREATMENT MODIFICATIONS IN RESPONSE TO IMMUNE-MEDIATED ADVERSE EVENTS

- The recommended dose of YERVOY is 3 mg/kg administered intravenously over 90 minutes every 3 weeks for a total of 4 doses

YERVOY (ipilimumab)–Dose Modifications

ADVERSE REACTION	WITHHOLD YERVOY FOR ANY OF THE FOLLOWING:	PERMANENTLY DISCONTINUE YERVOY FOR ANY OF THE FOLLOWING:
Immune-Mediated Enterocolitis	Grade 2 enterocolitis	Grade 3 or 4 enterocolitis
Immune-Mediated Hepatitis	AST or ALT >2.5x ULN to ≤5x ULN or total bilirubin >1.5x ULN to ≤3x ULN	AST or ALT >5x ULN or total bilirubin >3x ULN
Immune-Mediated Dermatitis	Grade 2 dermatitis	Grade 3 or 4 dermatitis
Immune-Mediated Neuropathies	Grade 2 neuropathy	Grade 3 or 4 neuropathy

- Withhold YERVOY for any other moderate (Grade 2) immune-mediated adverse reactions or for symptomatic endocrinopathy until return to baseline, improvement to mild severity, or complete resolution, and patient is receiving <7.5 mg prednisone or equivalent per day
- Permanently discontinue YERVOY for:
  - Persistent Grade 2 adverse reactions or inability to reduce corticosteroid dose to 7.5 mg of prednisone or equivalent/day
  - Failure to complete a full treatment course within 16 weeks from administration of the first dose
  - Any severe (Grade 3) or life-threatening (Grade 4) adverse reactions, including any of the following:
    - Colitis with abdominal pain, fever, ileus, or peritoneal signs; increase in stool frequency (≥7 over baseline), stool incontinence, need for intravenous hydration for >24 hours, gastrointestinal hemorrhage, and gastrointestinal perforation
    - AST or ALT >5 × ULN or total bilirubin >3 × the ULN
    - Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration or necrotic, bullous, or hemorrhagic manifestations
    - Severe motor or sensory neuropathy, Guillain-Barré syndrome, or myasthenia gravis
    - Severe immune-mediated reactions involving any organ system
    - Immune-mediated ocular disease that is unresponsive to topical immunosuppressive therapy

APPENDIX 9: Multicenter Institutional Studies

Data and Safety Monitoring Plan for Multicenter Study (Phase 2 or 3 Institutional Study)

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and subject safety for all HDFCCC institutional clinical studies. A summary of DSMC activities for this study include:

- Review of subject data
- Review of suspected adverse reactions considered "serious"
- Monitoring every six months (depending on study accrual)
- Minimum of a yearly regulatory audit

Monitoring and Reporting Guidelines

All institutional Phase 2 or 3 therapeutic studies are designated with a moderate risk assessment. The data is monitored every six months, with twenty percent of the subjects monitored (or at least three subjects if the calculated value is less than three).

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate quarterly conference calls with the participating sites to communicate the review of adverse events, safety data, and other study matters.

The Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress at all participating sites. The Study Chair will conduct continuous review of data and subject safety and discuss each subject's treatment at monthly UCSF Site Committee meetings. The discussions are documented in the UCSF Site Committee meeting minutes.

Multicenter communication

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate, at minimum, quarterly conference calls with the participating sites or more frequently as needed to discuss risk assessment. The following issues will be discussed as appropriate:

- Enrollment information
- Adverse Events (i.e. new adverse events and updates on unresolved adverse events and new safety information)
- Protocol Violations
- Other issues affecting the conduct of the study

Adverse events reporting to the DSMC will include reports from both the UCSF Coordinating Center, as well as the participating sites. The DSMC will be responsible for monitoring all data entered in OnCore® at the UCSF Coordinating Center and the participating sites. The data (i.e., copies of source documents) from the participating sites will be sent electronically to the UCSF Coordinating Center prior to the monitoring visits in order for the DSMC to remotely monitor the participating site's compliance with the protocol, patient safety, and to verify data entry.

Adverse Event Review and Monitoring

All grade(s) 3-5 adverse events, whether or not unexpected, and whether or not considered to be associated with the use of the study drug, will be entered into OnCore®, UCSF's Clinical Trial Management System.

All Grade 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the UCSF Site Committee meetings. All clinically significant adverse events must be reported to the UCSF Coordinating Center by the participating sites within 10 business days of becoming aware of the event or during the next scheduled quarterly conference call, whichever is sooner. The UCSF Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s) from the UCSF Coordinating Center and the participating sites.

In addition, all suspected adverse reactions considered "serious" must be entered in OnCore® and reported to the UCSF Coordinating Center within 1 business day. The suspected adverse reactions considered "serious" will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at the DSMC meeting, which take place every six (6) weeks.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and is determined to be related either to the investigational drug or any research related procedure, the Study Chair at the UCSF Coordinating Center or the assigned designee must be notified within 1 business day from the participating site(s) and the Study Chair must then notify the DSMC Chair or qualified alternate within 1 business day of this notification. The contact may be by phone or e-mail.

Increase in Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Study Chair at the UCSF Coordinating Center is responsible for notifying the DSMC at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Study Chair stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Manager must be notified within 1 business day via e-mail. The DSMC must receive a formal letter within 10 business days and the IRB must be notified.

Data and Safety Monitoring Committee Contacts

DSMC Chair:	[redacted]	DSMC Monitors
Phone:	[redacted]	[redacted]
Email:	[redacted]	
Address:	[redacted] UCSF San Francisco, CA 94115	UCSF Helen Diller Family Comprehensive Cancer Center San Francisco, CA 94115

* DSMP approved by NCI 09/February2012

APPENDIX 10: UCSF Policy/Procedure for Required Regulatory Documents for UCSF Investigator-Initiated Oncology Clinical Trials with an Investigator held Investigational New Drug (IND)

Purpose

This policy defines the required Regulatory Documents for Single Site and Multicenter Investigator Initiated Oncology Clinical Trials at the Helen Diller Family Comprehensive Cancer Center (HDFCCC) where the Principal Investigator (PI) holds the IND.

Background

The International Conference on Harmonization (ICH) Good Clinical Practices (GCP) Guidelines define Essential Regulatory Documents as those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of data produced. These documents serve to demonstrate compliance with standards of GCP and with all applicable regulatory requirements. Filing essential documents in a timely manner can greatly assist in the successful management of a clinical trial.

The Regulatory Documents will consist of electronic files in both iMedRIS and OnCore®, as well as paper files in the Regulatory Binders for both the Coordinating Site and the Participating Site(s) in the HDFCCC Investigator Initiated Oncology Clinical Trials.

Procedures

1. HDFCCC Essential Regulatory Documents

Documents Filed in iMedRIS:

- IRB approvals for initial submission of application, all modifications, and continuing annual renewals
- Current and prior approved protocol versions with signed protocol signature page(s)
- Institutional Review Board (IRB) approval letters and Informed Consent Form(s) (ICF)
- Current and prior versions of the Investigator Brochure (IB).
- Serious Adverse Event Reporting
- Protocol Violations and Single Patient Exception (SPE) Reports to IRB with supporting fax documentation

Documents Filed in OnCore®:

- Package Insert (if the study drug is commercial) or Investigator Brochure
- Protocol Review Committee (PRC) approved protocols, protocol amendments and Summary of Changes (SOC)
- Patient handouts
- Screening/enrollment log
- Data and Safety Monitoring Committee (DSMC) monitoring reports
- OnCore® Case Report Form (CRF) completion manual

Documents Filed in Regulatory Binder:

- Completed Food and Drug Administration (FDA) 1572 document with Study Chair's signature
- For all Study Chair and Sub-Investigators listed on the FDA 1572, will need Financial Disclosure Forms, CVs, MD Licenses, Drug Enforcement Agency (DEA) Licenses, and Staff Training Documents (i.e. Collaborative Institute Training Initiative (CITI), etc.)
- Site Initiation Visit (SIV) minutes and correspondence with participating site(s).
- As applicable, approvals for Biosafety Committee, Radiation Committee, and Infusion Center
- Serious Adverse Event (SAE) reports to IRB and sponsor.
- MedWatch reporting to sponsor
- Delegation of Authority Form
- Drug Destruction Standard Operating Procedure (SOP)
- For all laboratories listed on the FDA 1572, will need CLIA certifications, CAP certifications, lab licenses, CVs of Lab Directors, and laboratory reference ranges

2. Additional Essential Documents for Multicenter Trials for the Coordinating Center (filed in Regulatory Binder or OnCore)

- Institutional Review Board (IRB) approval letters, IRB roster, Informed Consent Form (ICF), and Health Insurance Portability and Accountability Act (HIPAA) Consent Form for the Participating Site(s)
- For all Principal Investigators and Sub-Investigators listed on the 1572 at the Participating Site(s) – Financial Disclosure Forms, CVs, MD Licenses, and Staff Training documents (i.e. Collaborative Institute Training Initiative (CITI), etc.) for Investigational New Drug Application
- Site Initiation Visit (SIV) minutes and correspondence with Participating Site(s).
- As applicable, approvals for Biosafety Committee, Radiation Committee, and Infusion Center for the Participating Site(s)
- Protocol Violations and Single Patient Exception (SPE) reports to IRB with supporting fax documentation for Participating Site(s)
- Drug Destruction Standard Operating Procedure (SOP) for the Participating Site(s)
- Data and Safety Monitoring Committee (DSMC) monitoring reports for the Participating Site(s)
- For all laboratories listed on FDA 1572, will need CLIA certifications, CAP certifications, lab licenses, CVs of Lab Directors, and laboratory reference ranges for the Participating Site(s)
- Copy of the Data and Safety Monitoring Plan (DSMP) Monitoring Plan for all participating site(s) in Multicenter studies or Contract Research Organization (CRO) Monitoring Plan (if an outside CRO is used for the study)
- Serious Adverse Event (SAE) forms submitted to both the IRB and the sponsor for the Participating Site(s)

Required Regulatory Documents for Sub-sites Participating in a UCSF Investigator Initiated Multicenter Trial (Checklist)

Directions:

1) Fax the documents listed below to the UCSF Coordinating center [redacted] *or*

2) Scan the documents and upload to OnCore® and create a Note to File for the on-site Regulatory binder to indicate where these documents may be found

1572

☐ PI and Sub investigators:

CV and Medical license

Financial disclosure form

NIH or CITI human subject protection training certification

☐ Laboratories

CLIA and CAP

CV of Lab Director and Lab Licenses

Laboratory reference ranges

Local Institutional Review Board

☐ IRB Approval letter

☐ Reviewed/Approved documents

- Protocol version date: _____
- Informed consent version date: _____
- Investigator Brochure version date: _____
- HIPAA

☐ Current IRB Roster

Other

☐ Delegation of Authority Log

- Include NIH or CITI human subject protection training certificates or GCP training certification

☐ Pharmacy

- Drug destruction SOP and Policy

☐ Protocol signature page

☐ Executed sub contract

APPENDIX 11: DENDREON SAE FORM

Dendreon

SERIOUS ADVERSE EVENT FORM

FAX TO DENDREON DRUG SAFETY WITHIN 24 HOURS OF BECOMING AWARE OF EVENT: 206-829-1647

Section 1a

PROTOCOL #: _____

SUBJECT #: _____

SUBJECT INITIALS: ☐☐☐

INITIAL REPORT DATE: ____/____/____ (MM DD YY)

SUBJECT DATE OF BIRTH: ____/____/____ (MM DD YY)

FOLLOW-UP REPORTS: #1 DATE: ____/____/____ #2 DATE: ____/____/____ #3 DATE: ____/____/____ (MM DD YY)

Section 2

Date site became aware of event: ____/____/____ (MM DD YY)

Principal Investigator: _____ (print name)

Institution: _____ City/State: _____ Country: _____

Form completed by: _____ (print name) Telephone: _____ Fax: _____

Section 3

SIPULEUCEL-T INFUSION DATE(S): ____/____/____ (MM DD YY) ____/____/____ (MM DD YY) ____/____/____ (MM DD YY)

OTHER PRODUCT: _____ ☐ NA DOSE: _____ First Dose: ____/____/____ (MM DD YY) Most Recent Dose: ____/____/____ (MM DD YY)

Section 4a

IF SUBJECT WAS HOSPITALIZED

Attach Discharge Summary when available

Check One: ☐ New ☐ Prolonged

Admission date: ____/____/____ (MM DD YY) Discharge date: ____/____/____ (MM DD YY)

Section 4b

IF SUBJECT EXPIRED

Attach Death Certificate when available

Autopsy performed? ☐ Yes ☐ No

Date of Death: ____/____/____ (MM DD YY) Autopsy results available? ☐ Yes ☐ No

Section 5

SERIOUS ADVERSE EVENT TERM OR DIAGNOSIS NOTE: If more than one event term is required for this report, please list each event term separately. All event terms must be recorded on the Adverse Event CRF.	ONSET DATE MM/DD/YY	RESOLUTION DATE MM/DD/YY	[1]SERIOUSNESS enter all that apply	[2]RELATIONSHIP TO PRODUCT enter only one	[3]OUTCOME enter only one

Section 6

USE THESE CODES IN THE COLUMNS ABOVE:

[1]SERIOUSNESS
1: Death
2: Life Threatening
3: Hospitalization
4: Disability
5: Congenital Anomaly
6: Medically Significant Intervention

[2]RELATIONSHIP TO PRODUCT
1: None
2: Possible
3: Probable

[3]OUTCOME
1: Recovered/Resolved
2: Recovering/Resolving
3: Recovered with Sequelae
4: Not Recovered/Not Resolved
5: Fatal (please fill in section 4b)
6: Unknown

Dendreon

SERIOUS ADVERSE EVENT FORM

FAX TO DENDREON DRUG SAFETY WITHIN 24 HOURS OF BECOMING AWARE OF EVENT: 206-829-1647

Section 1b

SUBJECT #: _____

SUBJECT INITIALS: ☐☐☐

Section 7

CASE NARRATIVE:

Describe the SAE. Include presenting signs and symptoms, clinical cause of the event, treatment of the event, and any other assessments which help explain the event. Give duration of the event if it persisted for less than 24 hours. State whether the event is or is not related to the apheresis procedure or investigational product infusion.

Section 8

OTHER RELEVANT HISTORY, TESTS OR LABORATORY DATA, CONCOMITANT MEDICATIONS OR THERAPY:

For example: cancer, allergies or concurrent illnesses. Attach relevant laboratory and imaging results. Attach updated Concomitant Medications CRF.

Section 9 **INITIAL REPORT**

INVESTIGATOR SIGNATURE: _____

DATE: ____/____/____ (MM DD YY)

FOLLOW-UP REPORTS

INVESTIGATOR INITIALS: _____ DATE: ____/____/____

INVESTIGATOR INITIALS: _____ DATE: ____/____/____

INVESTIGATOR INITIALS: _____ DATE: ____/____/____ (MM DD YY)

APPENDIX 12: IRRC TUMOR MEASUREMENT FORM

CC#12257 Ipi- Provenge (Phase 2) - Tumor Assessment Form Protocol version date: March 26, 2014

Name:	Subject ID:	MRN:	DOB:

Immune- related Response Criteria Instructions

- Measurable Disease/Target Lesions: longest diameter (LD) and longest perpendicular (LP), must be ≥20 mm with conventional techniques or ≥10mm with spiral CT scan.
- Non-measurable disease/Non-Target Lesions: all other lesions that do not qualify as target lesions, including small lesions, longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan and truly non-measurable lesions such as bone lesions)
- Add up to a maximum of 5 lesions per organ and 10 lesions total, representative of all involved organs
- LD(cm)x LP(cm)= PD(cm^2):Longest diameter x longest perpendicular = product of perpendicular diameters (PPD).
- SPD: Sum of products of the two largest perpendicular diameters.
- At each subsequent tumor assessment, the SPD of the index lesions and of new measurable lesions (≥5 x 5mm; up to 5 new lesions per organ, 10 visceral lesions) are added together to provide the total tumor burden.

Tumor Burden = $SPD_{index\ lesions}$ + $SPD_{new\ measurable\ lesions}$

- New non- measurable lesions should be added to non-measurable index lesions.
- Target lesions overall response **(CR, PR, and PD must be confirmed by a repeat, consecutive assessment no less than 4 wks from the date first documented)**:
  - Complete Response (CR): disappearance of all lesions (whether measurable or not, and no new lesions)
  - Partial response (PR): decrease in tumor burden ≥50% relative to baseline
  - Stable Disease (SD): not meeting criteria for CR or PR, in absence of PD
  - Progressive Disease (PD): increase in tumor burden ≥25% relative to nadir
- Non-target lesions overall response
  - CR: The disappearance of all non-target lesions
  - IR/SD: the persistence of one or more non-target lesion(s) without unequivocal progression of existing non-target lesions
  - PD: the appearance of one more or more new lesions and/or unequivocal progression of existing non-target lesions. For bone scans, the appearance of 2 or more new lesions is required These lesions should be re-evaluated 6 or more weeks later to confirm PD

		BASELINE	DAY 64	DAY 148	DAY 232
	Date:				
TARGET LESIONS					
#	Location / Method of Measurement	LD x LP = PPD	LD x LP = PPD	LD x LP = PPD	LD x LP = PPD
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
*Tumor Burden = $SPD_{index\ lesions}$ + $SPD_{new\ measurable\ lesions}$	Sum of PPD (SPD)/ Tumor Burden*				
	% change:	N/A			
NON-TARGET LESIONS					
#	Location / Method of Measurement	BASELINE	DAY 64	DAY 148	DAY 232
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
OVERALL RESPONSE ASSESSMENT (circle one)		N/A	CR IR/SD PD	CR IR/SD PD	CR IR/SD PD