A Phase II Study of CTLA Blockade by Ipilimumab plus Androgen Suppression Therapy in Patients with an Incomplete Response to AST Alone for Metastatic Prostate Cancer

OHSU PROTOCOL NUMBER: 5254
PCCTC PROTOCOL NUMBER: 08-004
BMS PROTOCOL NUMBER: CA184059

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Original Protocol Version/Date: *6/1/2011*
Protocol Revision Date: *6/30/14*

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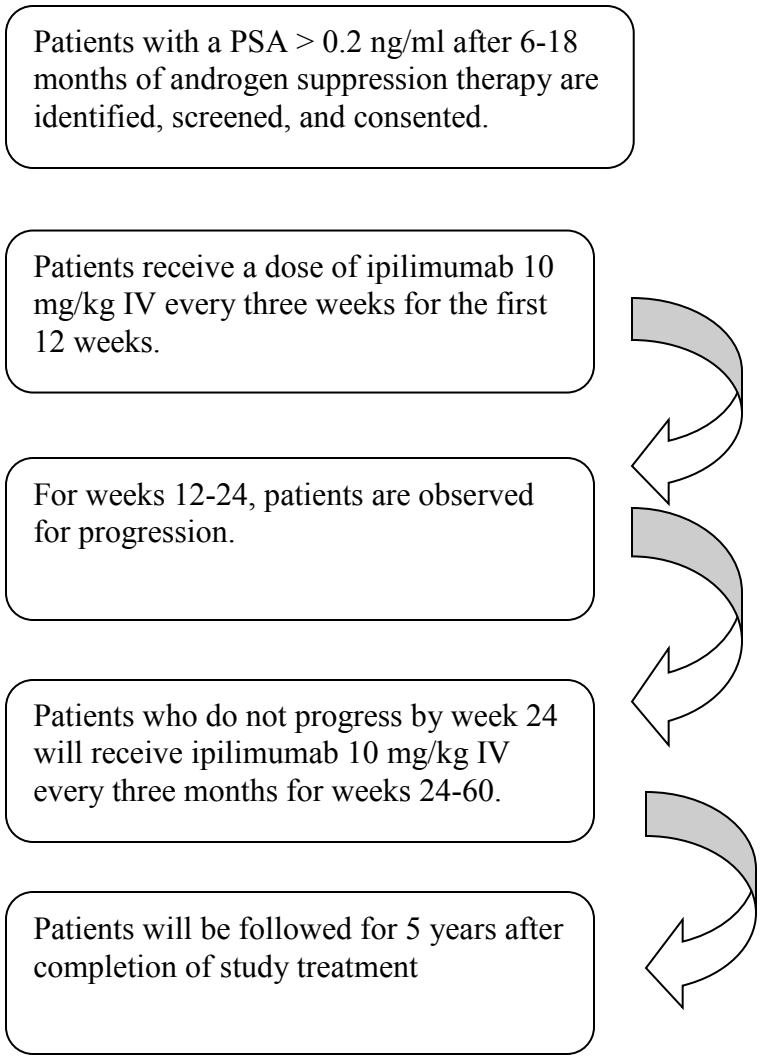
STUDY SCHEMA



PROTOCOL SYNOPSIS

Protocol Title:	A Phase II Study of CTLA Blockade by Ipilimumab plus Androgen Suppression Therapy in Patients with an Incomplete Response to AST Alone for Metastatic Prostate Cancer
Site Numbers & Names:	This study is currently open at Oregon Health & Science University and Rutgers Cancer Institute of New Jersey.
Research Hypothesis:	The early addition of immunotherapy in patients with metastatic prostate cancer who have a poor prognosis as a result of an incomplete biochemical response to androgen suppression therapy (AST) will improve outcomes to approximate outcomes in patients who do obtain a complete biochemical response with AST.
Study Schema: **Drugs / Doses / Length of Treatment)**	All patients will receive ipilimumab 10 mg/kg by 90-minute IV infusion every three weeks for four doses. Patients without progression at Week 24 will subsequently receive maintenance ipilimumab 10 mg/kg IV every 12 weeks for four additional doses. Patients will have their PSA checked every three weeks during the first four doses of ipilimumab, every six weeks between weeks 12 and 24, and every 12 weeks thereafter. Once all eight doses of ipilimumab have been given, patients will be followed with a serum PSA every 12 weeks (either at the research site or at the patient's treating physician) until radiographic progression. Survival status will be assessed by telephone every 6 months for as long as patients are alive for up to 5 years after their last study visit. There will be a CT scan of the chest/abdomen/pelvis and whole body bone scans at baseline, 12 weeks, 24 weeks, and then every three months until radiographic progression. Scans may be performed sooner if there are any concerns about progression. Correlative study labs will be drawn just prior to ipilimumab administration during the first four doses (weeks 1, 4, 7, 10).

Study Objectives:	The **primary endpoint** is the proportion of patients who achieve an undetectable PSA (≤ 0.2 ng/ml) after initiation of ipilimumab therapy. **Secondary endpoints** include time to PSA progression, time to disease progression by any measure, time to death from any cause, maximum percentage of PSA reduction in each patient, response in measurable disease by RECIST criteria, measure of T cell response by flow cytometry, number of patients with immune related Adverse Events (IRAEs) and correlation between IRAEs and clinical outcomes. The effect of treatment on the ratio of T regulatory cells to T effector cells and additional measures of immune response will also be determined. To examine correlative biomarkers and their relationship to clinical outcomes. Potential biomarkers include, but are not limited to CRP, IGF-1 and –2, or FSH.
Study Design:	This is a single arm phase II study to examine the activity of ipilimumab plus AST early in metastatic prostate cancer in men with an incomplete response to androgen suppression therapy (AST).
Accrual Goal:	30 patients
Accrual Rate:	1 to 2 patients per month
FPFV: **LPFV:** **Follow Up:**	Recruitment projected to begin 9/2011 Final patient registration projected for 6/2016 Follow-up for survival will continue for up to 5 years after the last subject ends the study.
Correlative Studies:	We will examine the T cell activation markers (HLA-DR, CD25, CD26, CD40L, CD62L, CD69, CD71, CD134) as well as the ratio of T effector to T regulatory cells before and after treatment with ipilimumab. These tests will be performed in the immunology laboratory of Larry Fong, MD, at UCSF. We will also examine antigens and correlate with response.

Inclusion Criteria:	Men with histologically confirmed adenocarcinoma of the prostate and radiographically documented metastases treated with AST who have a serum PSA > 0.2 ng/mL after 6 to 18 months of AST. Eligible patients must also have a documented white blood cell (WBC) count ≥ $2x10^9$/L, absolute neutrophil count (ANC) ≥ $1.0x10^9$/L, a platelet count ≥ $50x10^9$/L, hemoglobin ≥ 8 g/dL, aspartate aminotransferase (AST) ≤ 2.5 x ULN, a serum creatinine ≤ 3.0 times institutional ULN, bilirubin ≤ 3 x ULN unless diagnosed with Gilbert's syndrome and an ECOG performance status ≤ 1.
Exclusion Criteria:	Patients with a life expectancy less than 6 months, treatment with any investigational agent in the last 28 days, more than 18 months since initiation of AST, or a concurrent active malignancy diagnosed within the last 5 years (other than non-melanoma skin cancer, or other readily treatable tumors with expected cure) will not be eligible for this study. Patients must not have a known autoimmune disease, use prednisone > 10 mg daily (or its equivalent) orally for any indication, or have chronic infections (including hepatitis B or C or HIV).
Criteria for Evaluation: **(Efficacy, safety, stopping rules, etc.)**	Patients will receive a history and physical exam and multiple laboratory tests (PSA, complete chemistry panel and blood counts, as well as tests for endocrinopathies) at baseline and every 3 weeks during the first 4 doses of therapy. Available labs (i.e. the chemistry panel and blood counts) will be reviewed prior to administration of ipilimumab. Imaging studies will be done at baseline, 12 weeks, 24 weeks and then every six months, or sooner if concerning symptoms arise. If there is no evidence of radiographic progression on the 24-week scan, patients will go on to receive four doses of maintenance ipilimumab therapy (weeks 24, 36, 48, 60). They will have a history and physical exam at least every three months. Their survival status will be assessed by phone survey every 6 months for up to five years after the last study visit. Efficacy will be based on the results of the PSA and imaging studies (using PCWG2 and modified RECIST criteria). Safety will be monitored using the regular physician examinations and laboratory assessments.

Statistics:	N=30 (for the final analysis, 10 for the intial analysis). Using the Simon two-stage design for Phase II trials, the initial accrual will be 10 patients. Assuming that 10% of patients receiving usual care will achieve an undetectable PSA without additional intervention, the trial has a 80% power to detect a rate of achieving an undetectable PSA of ≥ 30% among patients treated with ipilimumab. At least two patients with an undetectable PSA will be required in the first 10 patients to continue to stage 2. As soon as two patients achieve an undectable PSA, stage 2 for of the study will begin. If 6 or more of 30 patients have achieved an undetectable PSA at 6 months, the study will be considered successful and the regimen worthy of further investigation. This design has a type I error rate of 0.05 and a type II error rate of 0.20. Demographic and clinical characteristics will be summarized using descriptive statistics (e.g. proportions, mean, standard deviation, median, range). The proportion of patients who achieve an undetectable PSA (≤0.2 ng/ml) after initiation of ipilimumab therapy will be provided with the exact 95% confidence interval. The Kaplan-Meier method will be used to estimate time to PSA progression, time to disease progression by any measure and time to death from any cause. In evaluation of time to PSA progression and time to disease progression by any measure will be censored for: (1) lost to follow-up at the date of last contact, (2) use of additional cancer therapies that would interfere with ascertainment of the endpoint of interest (3) death from causes other than prostate cancer or treatment of prostate cancer. Evaluation of time to death will be censored for lost to follow-up at last contact. The effects of IRAEs and other immune parameters (e.g., a ratio of T regulatory cells to T effector cells) on clinical outcomes will be evaluated using logistic regression for binary endpoints (e.g., achievement of undetectable PSA) and Cox regression for the time to event outcomes (e.g., time to PSA progression).

1 INTRODUCTION

1.1 Research Hypothesis

The early addition of immunotherapy in patients with metastatic prostate cancer who have a poor prognosis as a result of having an incomplete biochemical response to androgen suppression therapy will improve outcomes to resemble outcomes seen in those patients who do obtain a complete biochemical response with AST alone.

1.2 Product Development Rationale

In 2009, an estimated 27,360 men in the United States died from advanced metastatic prostate cancer, making prostate cancer the second most lethal malignancy among US men.[1] Also, an estimated 192,280 men were diagnosed with prostate cancer, and around 7,700 of those men had incurable disease (i.e., metastatic) at diagnosis.[1] Androgen suppression therapy (AST) is the most effective systemic therapy for these patients with incurable prostate cancer. Currently, the most promising approach to extending survival and protecting quality of life in these men is to identify ways to enhance the depth and duration of response to AST.

In a 2006 publication, Hussain, et al., examined outcomes in 1,345 such patients.[2] As shown below, the PSA nadir maintained after 6 to 7 months of AST was a powerful predictor of overall survival. Those patients who achieved an undetectable PSA fared best. The definition of undetectable PSA in this paper was a PSA ≤ 0.2.

PSA (ng/mL)	Number of Patients	Median Survival (months)
>4	383	13 (95% CI, 11-16)
≤4, >0.2	360	44 (95% CI, 39-55)
≤0.2	602	75 (95% CI, 62-91)

Hussain and colleagues were able to discriminate between men at high and low risk of dying from castration resistant prostate cancer (CRPC) at a point in the disease process when the disease burden is minimal. This discovery creates a novel opportunity to target this minimal volume androgen-independent disease early with the hope of altering the grim natural history of this disease state. Hussain's data also demonstrate that a complete PSA response to initial therapy is likely a pre-requisite for long-term survival.

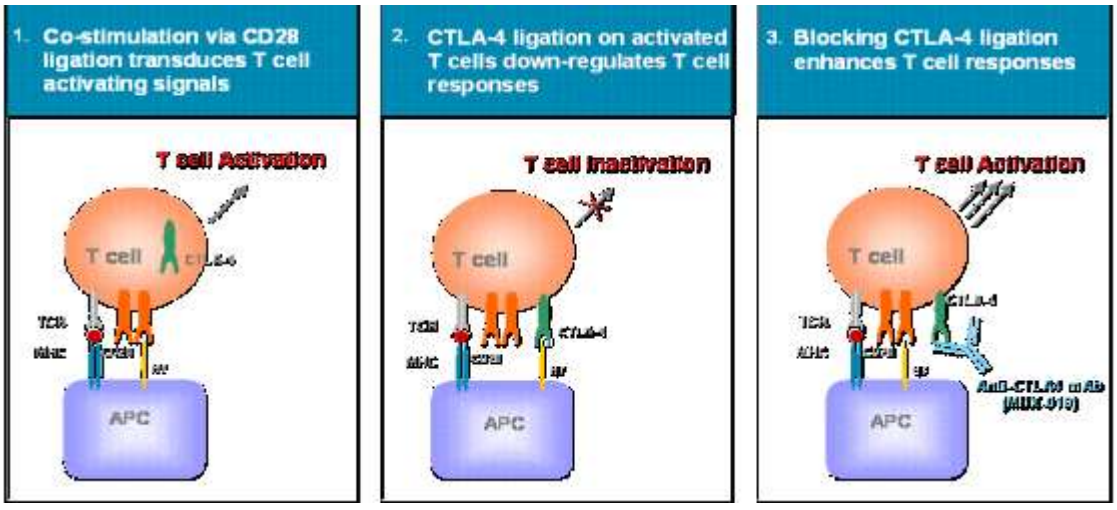
An emerging class of agents that target immune functions has shown promise in treating advanced prostate cancer. It is believed that cancer cells can evade immune detection by

interacting with the CTLA-4 receptor on the T cells. This interaction downregulates the immune response, thus allowing cancer cells to escape detection.[3] Immunotherapy with anti-CTLA antibody (ipilimumab) shows promise in Phase I studies of men with CRPC who have progressed through current therapeutic options.[4] At our institution, twenty-six metastatic prostate cancer patients have started this therapy. Of thirteen evaluable patients, four have had confirmed PSA responses (PSA decrease of 50% or greater from reference value confirmed by a second measurement at least 3 weeks later), including one with objective radiologic as well as PSA complete response, ongoing for over 2 years as of September 2009. Notably, these patients responded despite having considerably more extensive and more heavily pre-treated disease than the population targeted in this proposal.

We are collaborating with Lawrence Fong, an oncologist with an interest in prostate cancer immunology at USCF. All correlative studies will be done in Dr. Fong's laboratory. The total amount of blood required for these studies is 60 ml just prior to the first four ipilimumab doses (weeks 1, 4, 7, 10). We will perform correlative studies examining the ratio of T effector to T regulatory cells before and after treatment with ipilimumab.Dr. Fong's lab has identified its own set of prostate cancer antigens. The names of these antigens are not specifically outlined because they are proprietary at this time. The results of all studies will be correlated with outcomes and side effects in exploratory analyses.

1.2.1 CTLA-4 and T Cell Activation

Figure 1 Mechanism of Action



Advances in the understanding of the mechanisms that regulate T cell activation have allowed the rational design of new strategies for immunotherapy of tumors, including melanoma. It has been known for some time that engagement of the T cell antigen receptor by itself is not sufficient for full T cell activation; a second co-stimulatory signal is required for induction of IL-2 production, proliferation and differentiation to effector function of naive T cells. Abundant data now indicate that the primary source of this costimulation is mediated by engagement of CD28 on the T cell surface by members of the B7 family on the antigen-presenting cell (APC).[5] (See Figure 1.)

Expression of B7 has been shown to be limited to "professional" antigen presenting cells; that is, specialized cells of the hematopoietic lineage, including dendritic cells, activated macrophages, and activated B cells. It has been suggested that this sharply-defined restriction of B7 expression is a fail-safe mechanism for maintenance of peripheral T cell tolerance, insuring that T cell activation can only be stimulated by appropriate APCs.[6] The fact that tumor cells do not express B7 contributes to their poor capacity to elicit immune responses.[7,8]

The demonstration that induction of expression of B7 on many tumor cells by transfection, transduction, or other mechanisms can heighten tumor immunogenicity led to great interest in pursuing this as an approach to tumor immunotherapy. As demonstrated *in vivo* in murine tumor models, the utility of B7 expression as a vaccination approach is limited by the following factors: (1) B7-expressing tumor cell vaccines are only effective when the tumor cells have a high degree of inherent immunogenicity; (2) while B7-expressing vaccines have been shown in many cases to be effective in inducing protective immune responses, they have demonstrated only limited utility in inducing responses to established tumors; and (3) inactivation of tumor cells by radiation has been shown to destroy the immuno-enhancing activity of the B7 gene product.[9,10]

In the past few years it has become apparent that co-stimulation is even more complex than originally thought. After activation, T cells express CTLA-4, a close homologue to CD28. CTLA-4 binds members of the B7 family with a much higher affinity than CD28.[11]Although there was initially some controversy as to the role of CTLA-4 in regulating T cell activation, it has become clear that CTLA-4 down-regulates T cell responses.[12] This was initially suggested by the following in vitro observations: (1) blockade of CTLA-4/B7 interactions with antibody enhanced T cell responses;

(2) cross-linking of CTLA-4 with CD3 and CD28 inhibited T cell responses; and (3) administration of antibodies to CTLA-4 in vivo enhanced the immune response to peptide antigens or superantigens in mice.[13,14,15,16] Blocking CTLA-4-B7 interaction while preserving signaling via CD28 resulted in enhanced T cell responses in vitro[14]

Perhaps the most convincing demonstration of the down-regulatory role of CTLA-4 came from examination of mice with a null mutation.[17,18,19] CTLA-4 knockout mice appear to have spontaneously activated T cells evident at approximately 1 week after birth, followed by rampant lymphoproliferation and lymphadenopathy. These mice die at approximately 3 weeks of age, either as a result of polyclonal T cell expansion and tissue destruction or as a result of toxic shock resulting from lymphokine production by the T cells. Since thymocyte differentiation and selection proceed normally in CTLA-4-deficient mice, the rampant T cell expansion that occurs in the mice indicates that CTLA-4 plays a critical role in down-regulating T cell responses in the periphery.[16]

1.3 Summary of Results of Investigational Program

1.3.1 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.

1.3.2 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 (CD)3-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.

1.3.3 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.

1.3.4 Clinical Safety with Ipilimumab

Ipilimumab immunotherapy is currently FDA-approved in patients with unresectable advanced melanoma (unresectable Stage III or Stage IV).

Ipilimumab has been administered to approximately 2633 patients with different cancers in 24 completed or ongoing clinical trials as of 31-Mar-2008 with a dose range between 0.3 mg/kg and 20 mg/kg. Most experience with ipilimumab exists at the 3 mg/kg and 10 mg/kg dose levels. Patients who received ipilimumab at 3 mg/kg were treated in clinical studies conducted early in the development program and received either a single or multiple injections. Intra-patient dose escalation indicated that patients who were unresponsive at the 3 mg/kg dose level may have responded to 9 mg/kg. Based on preliminary data on the 10 mg/kg dose level of ipilimumab, the ongoing clinical program investigating ipilimumab in metastatic melanoma utilizes the 10 mg/kg dose level with the expectation that 10 mg/kg will prove more beneficial than 3 mg/kg.

1.3.4.1 Details of Drug-Related Adverse Events

Drug-related adverse events (AEs) were reported in studies with ipilimumab as monotherapy as well as in combination studies with vaccines, cytokines or chemotherapy. The AE profile of ipilimumab is relatively well characterized, with most drug-related AEs being immune-related adverse events (IRAEs), which are considered to be associated with the mechanism of action of ipilimumab. The most common IRAEs are colitis and diarrhea, rash, pruritis, deficiencies of endocrine organs (pituitary, adrenal or thyroid), hepatitis, and uveitis. Rare complications are bowel perforations (~1%) resulting from underlying severe colitis, which have required surgical intervention.

1.3.4.2 Drug-Related Serious Adverse Events

Drug-related Grade 3 or Grade 4 serious adverse events (SAEs) include: rash/desquamation, pruritus, uveitis, speech impairment, abdominal pain, diarrhea/colitis, nausea/vomiting, transaminase elevation, adrenal insufficiency, panhypopituitarism and atrial fibrillation. Some of these events, such as rash/desquamation, pruritus, uveitis, diarrhea/colitis, transaminase elevation, adrenal insufficiency and panhypopituitarism, may represent drug induced IRAEs (see Section 4.3.4). Refer to the most recent version of the Ipilimumab Investigator Brochure for the latest update on SAEs.

Among subjects treated with ipilimumab 10 mg/kg, SAEs considered possibly, probably, or definitely related to study drug were reported for 26% of subjects (176/675). Drug

related SAEs reported in at least 1% of the 675 subjects at 10 mg/kg included diarrhea (10%), colitis (7%), vomiting (3%), dehydration (3%), autoimmune hepatitis (2%), hypopituitarism (2%), nausea (2%), abdominal pain (2%), pyrexia (2%), aspartate aminotransferase increased (1%), alanine aminotransferase increased (1%), and fatigue (1%).

1.3.5 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.

Approximately 60% of subjects developed any grade IRAEs which involved predominately the gastrointestinal (GI) tract, endocrine glands, liver, or skin. Based on data from the safety database, the number of subjects with serious IRAEs was approximately 15% (401/2633), including 8.2% for serious GI IRAEs (diarrhea and/or colitis), 2.2% of serious endocrinopathy (primarily hypophysitis/hypopituitarism), 2% of pericarditis and <1% of serious skin IRAEs. Bowel perforation was reported in approximately 1% of subjects. With few exceptions these IRAEs were clinically manageable and reversible with supportive care or corticosteroids. In responding patients, addition of corticosteroids does not appear to have a temporal relationship to change in objective tumor response.

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.

1.3.5.1 Drug-Related Deaths

Based on reports from the safety data base as of June 30, 2008, there have been reports of death (approximately 1% [28/3000]), 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.

1.3.5.2 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 in subjects with melanoma, including 0.3 vs 3 vs 10 mg/kg. Table 1 summarizes the overall IRAE frequencies by dose from CA184-022 based on safety data from the locked clinical database.

Qualitatively, the safety profile of ipilimumab at 10 mg/kg remains consistent with the low-dose safety profile in that most of the drug-related SAEs are characteristic of immune-related toxicity, and most of the IRAEs are reported in the GI, hepatic, and endocrine systems. However, the data presented in Table 1 suggest that the frequency of IRAEs in association with 10 mg/kg of ipilimumab at multiple doses is higher compared with the IRAE frequency reported for lower doses.

Table 1. Summary of Immune-Related AEs 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

1.3.5.3 Neuropathies

Isolated cases of motor neuropathy of an autoimmune origin have been reported among patients treated with ipilimumab. Two cases have been diagnosed as Guillain-Barre syndrome (GBS), only one of which was considered study related. As of July 2, 2008, 15 cases of neuropathy SAEs have been reported. Of these, 13 were assessed as unrelated to study therapy because alternative etiologies, including brain metastases, spinal cord compression, or aterial thrombosis, were identified in almost every case.

1.3.6 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. Based on preliminary results, ipilimumab is active in patients with advanced stage malignant melanoma. The objective responses observed with ipilimumab may be considered durable as they have occurred across a spectrum of doses and schedules.

Based on a preliminary analysis for study MDX010-15 involving ipilimumab 10 mg/kg multiple doses, 34.8% of patients (N = 23) were progression-free at 6 months and about 17.4% were progression-free at 1 year. In comparison, for Study MDX010-08 involving ipilimumab 3 mg/kg multiple doses, 10.8% patients (N = 37) had progression-free survival at 6 months and 8.4% at 1 year. Ipilimumab has also been studied in combination with chemotherapy (dacarbazine), melanoma vaccines (gp100), and cytokines (IL-2). Further details on clinical results can be found in the current version of the Ipilimumab Investigator Brochure.

The clinical benefit of ipilimumab extends to prostate cancer patients as well. A pilot trial looked at the safety and efficacy in 14 prostate cancer patients with bone metastases and varying prior treatment regimens of their prostate cancer.[Small, Clin Cancer Res, 2007]. Half had already received chemotherapy prior to enrollment in the trial. Four patients also had soft tissue disease. Each patient received a single dose of ipilimumab, 3 mg/kg IV. Two patients had a PSA decline of ≥ 50%, and each of those patients elected to receive a second dose of ipilimumab 3 mg/kg IV. Neither of those patients had soft tissue lesions that could be measured by RECIST criteria. Their PSA responses lasted for 135 and 60 days, respectively.

More recently, 45 patients with metastatic, castration-resistant prostate cancer were given ipilimumab 10 mg/kg every three weeks for four doses.[20] Twenty-nine of the patients received a single dose of radiation just prior to the first dose of ipilimumab. Of these 29 patients, 14 had no exposure to chemotherapy prior to ipilimumab treatment, and 15 had received chemotherapy prior to ipilimumab treatment. The use of chemotherapy was historical, and not part of this study. The patients with a PSA decline of ≥ 50% were more likely to be chemotherapy naïve. The results are in Table 2. Importantly, response to ipilimumab appears to be increased with this dose and schedule, over the 3 mg/kg x1.

Table 2. Summary of PSA decline in men with advanced prostate cancer who were treated with ipilimumab with and without radiation and who either had or had not been previously treated with chemotherapy.

Sub group	Ipi alone	XRT + Ipi No chemo	XRT + Ipi Chemo	All Ipi alone	All XRT + Ipi	All No Chemo	All Chemo
N (45 patients total	16	15	14	16	29	27	18
≥ 50% PSA↓	5	4	1	5	5	8	2

This study did not formally compare ipilimumab with radiation versus ipilimumab alone. The data presented in Table 2 does not overwhelmingly support or refute the usefulness of radiation added to ipilimumab.

1.3.6.1 Relationship Between Response and Immune Breakthrough Events in Patients with Metastatic Melanoma and Prostate Cancer

Drug-related AEs of any grade considered to be immune-mediated in nature (IRAEs) were reported for 54.0% of subjects in clinical studies of ipilimumab. These IRAEs are a consequence of inhibiting CTLA-4 function and most were reported as Grade 1 or 2. An association between BORR and higher grade (Grade 3-4) IRAEs was suggested in early studies of ipilimumab 3 mg/kg but this association was not observed in 4 Phase 2 studies of ipilimumab (CA184022, CA184008, CA184007 and CA184004). There were proportionally more subjects with IRAEs of any grade who experienced response or stable disease than subjects without IRAEs who experienced response or stable disease, but due to the small sample sizes, these observations were statistically inconclusive.[21,22,23]

1.4 Overall Risk/Benefit Assessment melanoma and prostate cancer

Results from the 3 primary efficacy studies of ipilimumab suggest that the 10 mg/kg dose is active and offers the best benefit to risk ratio based on a 27.1% to 35.1% rate of disease control and a favorable 1-year survival rate of 48.6% to 59.1% compared with that reported in the literature (25.5% to 35%).[24,25,26,27] Substantial reductions in total tumor burden, including widely disseminated disease in the skin, lung, and/or other visceral

disease sites, were reported. More than half the responses were reported in subjects staged with M1b or M1c advanced melanoma disease, which is most resistant to approved therapies. The kinetics of ipilimumab resulted in known patterns of clinical activity (CR, PR and SD) as well as novel patterns, characterized by reductions in total tumor burden, including existing and new lesions, after initial tumor volume increase and/or after appearance of new lesions. In the pretreated population at 10 mg/kg in 2 of the 3 studies, disease control after initial tumor volume increase and/or new lesions was reported for 9.7% of subjects. Across all 3 studies, stable disease was often accompanied by clinically relevant reductions in tumor burden compared to baseline. All patterns of response, including SD, appeared to result in favorable survival, based on 1-year survival rates.

Characteristic organ-specific inflammatory IRAEs were reported with ipilimumab therapy, typically during induction therapy. IRAEs were mostly reversible within days to weeks following cessation of therapy or treatment with symptomatic therapy, corticosteroids or other anti-inflammatory agents, depending upon severity. Accumulated clinical experience resulted in detailed toxicity management guidelines (also termed algorithms), by use of which IRAEs can be effectively managed, especially when IRAEs are recognized early and subjects are treated in a timely fashion. This can minimize the occurrence of IRAE complications, such as GI perforation/colectomy or hepatic failure.

Treatment with ipilimumab resulted in clinical activity in pretreated and previously untreated subjects with advanced melanoma. Clinically relevant reductions in the tumor burden from baseline were reported, together with a preliminary evidence of improved overall survival compared with published survival rates. These findings, together with evidence of a safety profile that is manageable with careful monitoring and appropriate intervention for treatment of immune-related toxicities, suggest an acceptable benefit to risk ratio.

Men with metastatic prostate cancer who do not obtain and maintain a complete biochemical response (PSA $\leq$ 0.2 ng/ml) to AST alone have a very poor prognosis.[2] The median survival of this study population is only 13 to 44 months, where a PSA > 4.0 ng/ml after induction AST has the shortest median survival. Chemotherapy using docetaxel with prednisone is currently an option for men with CRPC. While there have been no direct comparisons of toxicity between ipilimumab and docetaxel, we anticipate that the overall toxicity of chemotherapy is greater. Since the initial approval of this study, several other agents have gained approval in CRPC, namely abiraterone with

prednisone, enzalutamide and sipuleucel-T. Although they have been shown to improve overall survival, their benefit compared to placebo is on the order of 2-4 months, and there is still a clear need to improve survival in this group. Furthermore treatment with ipilimumab does not disqualify patients from being treated with these other agents.

The early identification of this aggressive subset of metastatic prostate cancer offers significant opportunities for benefit in the form of delayed progression and longer survival with successful intervention. The overall risk-benefit ratio for patients entering this protocol is therefore at least comparable to and possibly better than alternative options.

1.5 Study Rationale

Ipilimumab is a natural choice for early intervention for several reasons. While there can be significant toxicities during the acute phase of treatment, the toxicities are almost always manageable and resolve with time-limited treatment. Thus, long-term toxicities in men who benefit from this intervention are unlikely. Immunotherapy may be more effective when disease burden is limited. Treating this population early will ensure that they have a relatively low volume of disease. This therapy has been shown to be active in patients who have extremely aggressive disease. We are targeting the same patients but at an earlier time point in the course of their disease. The overall risk benefit ratio for patients entering this protocol is therefore at least comparable to, and possibly better than alternative options.

This is a single arm phase II study to examine the activity and safety of ipilimumab early in the course of metastatic prostate cancer, in patients with an incomplete response to androgen suppression therapy. Men who do not achieve a complete response to AST have a significantly shortened median survival. Early immune-based therapy may delay disease progression and prolong survival in this subset of patients.

The primary endpoint is the fraction of patients who achieve an undetectable PSA ($\leq$ 0.2 ng/ml). The Hussain paper has shown that men who achieve and maintain an undetectable PSA have a significantly longer median survival.[2] We will recruit 30 men to this study.

Secondary endpoints include time to PSA progression, time to progression by any measure, time to death from any cause, number of patients with immune breakthrough events and correlation of these with PSA declines and correlative studies looking at the

ratios of T regulatory cells and T effector cells before each of the first four doses of ipilimumab.

2 STUDY OBJECTIVES

2.1 Primary Objective

Proportion of patients who achieve an undetectable PSA (≤ 0.2 ng/ml) after initiation of Ipilimumab therapy.

2.2 Secondary Objectives

- Time to PSA progression
- Time to progression by any measure
- Maximum percentage of PSA reduction in each patient
- Number of patients with IRAEs and correlation of these with complete PSA response, time to progression, and T cell measurements
- Measures of T cell response to therapy with flow cytometry
- Response in Measurable disease by modified RECIST criteria
- Time to death from any cause.
- To examine correlative biomarkers and their relationship to clinical outcomes. Potential biomarkers include, but are not limited to CRP, IGF-1 and –2, or FSH.
- Bank samples for future molecular correlative studies, biomarker, or other studies.

3 STUDY DESIGN

3.1 Pre-treatment Evaluation

3.1.1 Clinical evaluation

- Patient's eligibility will be determined with the aid of an eligibility checklist.
- Eligible patients will be informed of the details of the study, including potential risks and benefits.
- Signed, informed consent will be obtained before any study-related procedures occur.

- A complete patient history and physical examination will be done.
- All concomitant medications including vitamins, herbs, and supplements will be recorded.

3.1.2 Laboratory

All screening labs must be done within 28 days of first treatment. Cycle 1 Day 1 labs do not need to be repeated if screening labs were within 7 days of Cycle 1 Day 1.

- Serum PSA .
- Complete Blood Count with automated differential
- Chemistry panel including ALT, AST, Alkaline Phosphatase, Total or Direct Bilirubin, BUN, Creatinine, Electrolytes (Sodium, Potassium and Chloride), Calcium, and Glucose
- Autoimmune panel including TSH and free T4
- LDH
- Testosterone
- Investigational blood samples will be obtained **within 0 to 7 days prior to treatment** (for the baseline) and just prior to each of doses of Cycle 2, 3, 4.
- Hepatitis panel and HIV will be tested if the study patient has engaged in high risk behaviors, such as using intravenous drugs or engaging in unprotected sex outside of a long term relationship. This determination will be made by the treating oncologist.

3.1.3 Imaging and Diagnostic

A radionuclide bone scan and CT scan (chest, abdomen and pelvis) will be obtained at baseline within 28 days of initiation of treatment.

3.2 Registration Procedure

A centralized registration procedure will be used. After eligibility screening, patients selected to participate will be registered with the lead center (OHSU) first, then their study site/institution.

3.2.1 **Lead Site Registration**: To initiate lead site registration, study sites/institutions should forward copies of the signed informed consent, HIPAA research authorization, the study registration form (eligibility checklist), plus all source documentation verifying eligibility, to the lead center by fax or e-mail. Upon receipt of these forms, sponsor will confirm patient eligibility with study personnel; assign a unique patient study identification number, and complete

patient registration. Treatment must not commence until the patient has received his identification number.

Patient Registration:
Erin Tucker, OHSU
Phone: (503) 494-8729
Fax: (503) 494-6197
Email: **TUCKERER@OHSU.EDU**

3.2.2 **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 HIPAA research authorization.

3.3 Follow up with Monitoring, Dose Delays and Dose Modifications

3.3.1 During the first four doses of ipilimumab treatment:

- Adverse events will be recorded every 3 weeks or as they occur.
- Physical examination and vital signs will be performed every 3 weeks and documented in the medical record.
- Complete Blood Count with automated differential, PSA, Chemistry Panel (Calcium, ALT, AST, Alkaline Phosphatase, Total Bilirubin, BUN, Creatinine, Glucose, Sodium, Potassium, Chloride) and Autoimmune Panel (,TSH, free T4) will be obtained on day 1 of the first four 21-day cycles.
- Available lab results will be reviewed prior to administration of ipilimumab.
- Imaging: A radionuclide bone scan and CT scan (chest, abdomen and pelvis) will be obtained at baseline, week 12, week 24, and every three months thereafter until radiographic progression. Scans may be obtained sooner for concerning symptoms.
- Correlation studies: Investigational serum samples will be obtained at baseline and on the first day of cycles 2 through 4. See Appendix 7 for details. Baseline draw will occur within 7 days of the first dose and must occur before the treatment dose is administered.

3.3.2 After Completion of initial 4 cycles of ipilimumab:

- Serum PSA will be drawn every 6 weeks for weeks 12-24, then every 12 weeks.
- Complete blood count with automatic differential, comprehensive chemistry panel and Autoimmune Panel (TSH, free T4) will be obtained prior to administration of each dose of ipilimumab, which will be given to eligible patients every 12 weeks beginning at week 24.

- Available lab results (i.e. chemistries and blood counts) will be reviewed prior to administration of ipilimumab.
- Imaging and Diagnostic: A radionuclide bone scan and CT scan (chest, abdomen and pelvis) will be obtained at baseline, week 12, week 24, and every three months thereafter until radiographic progression. Scans may be obtained sooner for concerning symptoms.

3.4 Correlative studies

Investigational blood samples will be obtained on the first day of cycles 1 through 4. Any specimens not consumed by the analyses in this protocol will be banked for future research in the Cancer Research Specimen Bank (OHSU IRB 2816). See Appendix 7 for details.

3.5 End of Treatment Cycles

Patients who progress radiographically on ipilimumab after completion of the initial four doses will not receive more immunotherapy once progression has been documented. For soft-tissue lesions, the RECIST criteria for progression (see 6.4.2) will be used. For bone lesions, there should be ≥ 2 new lesions confirmed on a second scan at least 4 weeks later. Progression will not be assessed until completion of the initial 4 cycles of treatment in order to avoid premature discontinuation of therapy.

3.6 Follow-up visits after completion of ipilimumab therapy

Patients will be followed with a history, physical exam, CT and NM bone scan and serum PSA quarterly along with treatment visits during the maintenance treatment phase, until radiographic progression. If a patient has not met radiographic progression by Week 60 visit, the patient will be followed by PSA and scans until radiographic progression. Following radiographic progression, patients will be followed by semi-annual phone surveys with the patient, his family, or his treating physician to collect data on treatment status and overall survival for up to 5 years after all protocol treatment has been completed.

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) Willing and able to give written informed consent.
2) Histologic diagnosis of adenocarcinoma of the prostate.
3) A PSA of > 0.2 ng/ml after 6-18 months of androgen suppression therapy, which may consist of LHRH agonist or antagonist alone or the combination of an LHRH agonist or antagonist plus an antiandrogen, such as bicalutamide. Androgen suppression therapy will continue without interruption.
4) Radiographic evidence of regional or distant metastasis at the time of study enrollment or at the time of diagnosis.
5) Required values for initial laboratory tests:
   - WBC ≥ 2000/uL
   - ANC ≥ 1000/uL
   - Platelets ≥ 50 x 10^3/uL
   - Hemoglobin ≥ 8 g/dL
   - Creatinine ≤ 3.0 x ULN
   - AST/ALT ≤ 2.5 x ULN for patients without liver metastasis
   - Bilirubin ≤ 3.0 x ULN, (except patients with Gilbert's Syndrome, who must have a total bilirubin less than 3.0 mg/dL)
6) No known active or chronic infection with HIV, Hepatitis B, or Hepatitis C. Patients should be assessed for high risk behaviors that may result in these infections, such as intravenous drug use or multiple sexual partners. The assessment should be noted.
7) ECOG ≤ 1.
8) Men ≥ 18 years of age.
9) Patients receiving any herbal product known to decrease PSA levels (i.e. saw palmetto and PC-SPES), or any immunosuppressive dose of systemic or absorbable topical corticosteroid (except prednisone up to 10 mg orally q day, or its equivalent), must discontinue the agent for at least 2 weeks prior to screening. Progressive disease must be documented after discontinuation of these products.
10) Patients receiving bisphosphonate therapy must have been on stable doses for at least 4 weeks with stable symptoms prior to the first infusion with ipilimumab.

11) Total testosterone < 50 ng/ml, except in patients with prior orchiectomy, where testosterone does not need to be measured. Patients must continue their LHRH agonist therapy throughout study duration.

12) Life expectancy ≥ 6 months. This must be documented.

13) Patients who are sexually active with a partner who could become pregnant are to use an effective form of barrier contraception, such as condoms or a partner using oral contraceptive pills. Persons of reproductive potential must agree to use an adequate method of contraception throughout treatment and for at least 8 weeks after ipilimumab is stopped.

14) If a patient enters the trial on AST that consists of both an LHRH agonist and an oral antiandrogen, both agents should be continued throughout the study. If an antiandrogen is stopped prior to study entry, it should be stopped 4 weeks before for nilutamide and flutamide and 6 weeks before for bicalutamide to ensure that a withdrawal phenomenon does not interfere with interpretation of efficacy results.

4.2 Exclusion Criteria

1) Radiation to any area of the body < 28 days prior to randomization.

2) Any other active malignancy with the exception of adequately treated basal or squamous cell skin cancer or superficial bladder cancer. Autoimmune disease: Patients with a history of inflammatory bowel disease are excluded from this study, as are patients with a history of symptomatic disease (eg, rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, autoimmune vasculitis [eg, Wegener's Granulomatosis]); motor neuropathy considered of autoimmune origin (e.g. Myasthenia Gravis, Guillain-Barre Syndrome). Those with immune-mediated skin toxicity (i.e. Toxic Epidermal Necrolysis, Stevens-Johnson Syndrome) will also be excluded.

3) 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) Any non-oncology vaccine therapy used for prevention of infectious diseases (for up to 1 month before or after any dose of ipilimumab).

5) A history of prior treatment with ipilimumab or prior CD137 agonist or CTLA-4 inhibitor or agonist.

6) Concomitant therapy with any of the following: IL-2, interferon, or other non-study immunotherapy regimens; cytotoxic chemotherapy; immunosuppressive

agents (OTC/herbal/prescribed); immunostimulant agents, other than the study agent; other investigational therapies; or chronic use of systemic corticosteroids (greater than prednisone 10 mg orally per day, or its equivalent).

7) Prisoners or patients who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (i.e., infectious) illness.

4.3 Data Safety Monitoring Plan

The Data and Safety Monitoring Plan is outlined in a separate document and is NCI approved.

5 STUDY THERAPY

All patients will receive ipilimumab 10 mg/kg IV over 90 minutes on day 1 of each 21-day cycle for four cycles. Those patients who have not progressed (radiographically) will also receive the same dose of ipilimumab once every three months for an additional four doses. **Each patient's available lab results (i.e. chemistries and blood counts) will be reviewed prior to each ipilimumab infusion**.

5.1 Ipilimumab

Each patient will receive ipilimumab 10 mg/kg IV over 90 minutes (not bolus or IV push).

Ipilimumab (BMS-734016) 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 nonspecific cross-reactivity in normal human tissues, as demonstrated by immunohistochemistry. Ipilimumab does cross-react with CTLA-4 in non-human primates, including cynomolgus monkeys.

5.1.1 Dose Calculations

Dose calculations will be based on the weight obtained on Cycle 1 Day 1 and will only change if the weight increases or decreases by more than 10%.

Calculate **Total Dose** as follows:

Patient body weight in kg x [10 mg] = total dose in mg

Calculate **Total Infusion Volume** as follows:

Total dose in mg ÷ 5 mg/mL = infusion volume in mL

Calculate **Rate of Infusion** as follows:

Infusion volume in mL ÷ 90 minutes = rate of infusion in mL/min.

For example, a patient weighing 114 kg (250 lb) would be administered 1140 mg of ipilimumab (114 kg x 10 mg/kg = 1140 mg) with an infusion volume of 228 mL (1140 mg ÷ 5 mg/mL = 228 mL) at a rate of approximately 2.5 mL/min (228 mL ÷ 90 minutes) in 90 minutes.

5.1.2 Storage, Preparation, and Administration

Ipilimumab Injection, 50 mg/vial (5 mg/mL) or 200 mg/vial (5 mg/mL), must be stored refrigerated (2°C to 8°C) and protected from light. Ipilimumab injection must not be frozen. Partially used vials or empty vials of Ipilimumab Injection should be discarded at the site according to appropriate drug disposal procedures.

Ipilimumab injection may be diluted in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to concentrations between 1 mg/mL and 4 mg/mL and stored in PVC, non-PVC or glass containers for up to 24 hours at 2-8ºC or RT/RL.

Recommended safety measures for preparation and handling include protective clothing, gloves, and safety cabinets.

5.1.2.1 Preparation and Administration Guidelines

The supplies needed for ipilimumab preparation and administration include calibrated syringes and infusion containers. The product may be infused using a volumetric pump at the protocol-specific dose(s) and rate(s) through a PVC IV solution infusion set with a 0.2 µm or 1.2 µm in-line polyethersulfone or 1.2 µm positively charged nylon filter to complete the infusion in 90 minutes, with a 10-mL normal saline flush at the completion of the infusion.

1) As ipilimumab is stored at refrigerated temperatures (2-8ºC), allow the appropriate number of vials of ipilimumab to stand at room temperature for approximately five minutes.
2) Aseptically withdraw the required volume of ipilimumab solution into a syringe. Insert the needle at an angle into the ipilimumab vial by placing the needle – bevel side down – against the glass, with the tip touching the neck of the vial. The initial solution concentration is 5 mg/mL. [Note: A sufficient excess of ipilimumab is incorporated into each vial to account for withdrawal losses].

3) Ensure that the ipilimumab solution is clear colorless, essentially free from particulate matter on visual inspection. If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall, etc.
4) Inject ipilimumab solution withdrawn into an appropriate size evacuated infusion bag to produce a final infusion volume that has been calculated from the weight of the patient. For example, if preparing a 10mg/kg treatment for a 65 kg patient you will use 13 vials (or 650 mg), the drug solution volume will be 10 mL per vial or 130 mL total.
5) If the total dose calculates to less than 90 mL of solution then the total dose needed should be diluted to a total volume of 90 mL in 0.9% sodium chloride.
6) Mix by GENTLY inverting several times. DO NOT shake.
7) Visually inspect the final solution. If the initial diluted solution or final dilution for infusion is not clear or contents appear to contain precipitate, the solution should be discarded.
8) Do not draw into each vial more than once. Any partial vials should be safely discarded and should not be stored for reuse.

Ipilimumab should be administered under the supervision of a physician experienced in the use of intravenous (IV) agents. Ipilimumab is administered as an IV infusion only.

5.1.3 Dose Modifications

Patients may develop study drug-related toxicities that may require skipping doses or dose discontinuation. Some of these adverse events may be consistent with potentially drug-related immune-mediated phenomena; termed IRAEs (Appendix 3). Details of how to dose study medication in the present of adverse drug reactions that may or may not be IRAEs are addressed below.

Treatment modifications will be made based on specified safety criteria. Patients will delay or discontinue treatment with ipilimumab if they experience at least one adverse event, specified below, considered by the investigator to be certainly, probably, or possibly related to ipilimumab treatment. The following criteria will be used to determine dosing delay, restarting doses, or discontinuing ipilimumab.

There are no dose modifications because Ipilimumab is much less effective at lower doses.

Delay ipilimumab dosing for the following related adverse events:

It may be necessary to skip study drug dosing for the following related adverse event(s):

- Any ≥ Grade 2 non-skin related adverse event (including IBEs), except for laboratory abnormalities
- Any ≥ Grade 3 laboratory abnormality.

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 3 weeks of initial dose administration:

- 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 the protocol-specified dosing window (3 weeks [+/- 3 days], the next scheduled dose will be *omitted*.

5.1.4 Discontinuation of Study Therapy

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
- Termination of the study by Bristol-Myers Squibb (BMS).
- Imprisonment or the compulsory detention for treatment of either a psychiatric or physical (e.g., infectious disease) illness.
- Progression of disease, as defined by radiographic progression, **after 12 weeks of therapy**. Furthermore, all radiographic progression must be confirmed by a repeat scan done at least 4 weeks after the suspicious scan. Immune response is not a part of this algorithm.

5.1.5 Permanent Discontinuation of Ipilimumab

5.1.5.1 Permanent Discontinuation for Related Adverse Events

- 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 under "No Discontinuation" (below).
- 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.

5.1.5.2 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.

5.1.6 Immune-Related Adverse Events (IRAEs): Definition, Monitoring, and Treatment

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. See Appendix 3 for suggested work-up and treatment of IRAEs.

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. See Appendix 4 for additional details.

5.1.7 Other Guidance

5.1.7.1 Immune-Related Adverse Events Considered to be Related to the ipilimumab

Previous studies have shown that 74% (about 3 in 4) of treated patients develop a side effect of any grade of severity due to the immune system attacking normal cells. About 22% (about 1 in 4) of patients have a serious immune-related adverse event. Serious side effects may be fatal or life-threatening, require you to be hospitalized, may permanently disable you, make you weak and unable to function at your current level, or may put your health at risk or require surgery or intervention by your study doctor.

These immune-related side effects have usually been controlled by stopping the ipilimumab treatment and if needed, with medications, including steroids (medications that are used to decrease inflammation). If you develop an immune-related event, the symptoms may take several months to improve. These immune-related adverse events can relate to: Stomach/Intestine, Rash, Eye, Endocrine Glands, Liver, Other Organs, Meningitis, immune-related motor neuropathy, nephritis, skin disorders and joint pain.

Patients receiving the Ipilimumab sometimes experience a serious skin toxicity, though this is very rare. If a patient develops a skin toxicity, a biopsy is recommended. If a biopsy is done, a portion of it may be sent to an independent doctor for review.

While receiving treatment with the ipilimumab, patients may be at risk of side effects (such as fever, low blood pressure, chills, flushing, nausea and/or vomiting) that occur during or shortly after the infusion (within 24 hours). If these events occur during the infusion, they may be treated by slowing or stopping the infusion, or with treatment such as fluids given into your vein or other common medications. These events can also occur hours after the completion of the infusion.

5.1.7.2 Treatment of Infusion Reactions Associated with Ipilimumab

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.

- 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 [mild symptoms] or below [severe symptoms] such as generalized pruritus, flushing, rash, dyspnea, 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 urticaria, 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).

5.1.7.3 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.

5.2 Prohibited and Restricted Therapies During the Study

5.2.1 Prohibited Therapies

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.

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
- CD137 agonists
- Immunosuppressive agents
- Immunostimulant agents, other than study medication
- Chronic systemic corticosteroids
- Any non-oncology vaccine therapies used for the prevention of infectious diseases (for up to 30 days prior to or after any dose of study drug).
- Any radiation therapies
- Any herbal product known to decrease PSA (eg, Saw Palmetto, PC-SPES)

5.2.2 Restricted Therapies

If a patient enters the trial on AST that consists of a LHRH agonist and an oral antiandrogen, both agents should be continued throughout the study. Patients entering the trial may have stopped previous AST before starting this study for various reasons including but not limited to: AEs related to AST therapy, disease progression on AST, or at the discretion of the treating physician. If an antiandrogen is stopped prior to study entry, it should be stopped 4 weeks before for nilutamide and flutamide and 6 weeks before for bicalutamide to ensure that a withdrawal phenomenon does not interfere with interpretation of efficacy results.

5.2.3 Precautions

Caution is advised when considering treatment with high-dose IL-2 in patients who have previously been administered ipilimumab, particularly in patients who experienced ipilimumab-related diarrhea/colitis. Colonoscopy or sigmoidoscopy with biopsy may be advisable prior to IL-2 administration once the patient is no longer receiving ipilimumab. Notably, IL-2 is not currently used for prostate cancer.

6 STUDY PROCEDURES AND OBSERVATIONS

6.1 Time and Events Schedule for Protocol CA184059

Test / Procedure	Screening[#]	Induction[*] (Cycles 1-4)				Between Treatments			Maintenance[*] (Cycles 5-8)				Every 6 Month Follow Up[*]
		Wk 1[**]	Wk 4	Wk 7	Wk 10	Wk 12	Wk 18	Wk 23/24	Wk 24	Wk 36	Wk 48	Wk 60	
Informed Consent	X												
Inclusion / Exclusion Criteria	X												
Demographics, medical history, concurrent medical conditions	X												
Testosterone level	X												
Serum samples for hepatitis panel and HIV, if high index of suspicion	X												
ECOG performance status	X	X	X	X	X	X	X	X	X	X	X	X	
Blood collection for correlative studies[1]		X	X	X	X								
Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	
Weight		X	X	X	X				X	X	X	X	
Bone Scan[2]	X					X		X		X	X	X	
Chest, Abdomen & Pelvis CT[2]	X					X		X		X	X	X	

CBC with differential	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry Panel: Creatinine, BUN, electrolytes (sodium, potassium, chloride), glucose, bilirubin alkaline phosphatase, ALT, AST, calcium, [3]	X	X	X	X	X	X	X	X	X	X	X	X	
LDH	X												
Autoimmune Profile: TSH, free T4	X	X	X	X	X				X	X	X	X	
PSA[4]	X	X	X	X	X	X	X	X	X	X	X	X	
Concurrent medications (include documentation of androgen suppression therapy)	X	X	X	X	X				X	X	X	X	
Adverse Effects Recorded	X	X	X	X	X				X	X	X	X	
Ipilimumab		X	X	X	X				X	X	X	X	
Telephone Contact													X

* Cycle 1-8 procedures can be done +/- 3 days and Long Term Follow-Up can be done +/- 2 weeks.

PSA, Autoimmune profile, LDH, CBC Diff, Chem panel including Creatinine, BUN, electrolytes (sodium, potassium, chloride), glucose, bilirubin, alkaline phosphatase, ALT, AST, calcium, phosphorus and Correlative **baseline samples DO NOT need to be repeated on Cycle 1 Day 1 if done within 7 Days of Cycle 1 Day 1

#Screening procedures must be done within 28 days of first treatment

[1] Per outlined correlative studies

[2] Imaging Studies will also be done every three months until radiographic progression

[3] Available labs (i.e. chemistries and blood counts) will be reviewed prior to each infusion

[4] PSA will be done until radiographic progression

6.2 Procedures by Visit

The Time and Events Schedule summarizes the frequency and timing of various measurements.

6.2.1 Study Completion or Early Discontinuation Visit

At the time of study early withdrawal, the reason for early withdrawal and any new or continuing adverse events should be documented.

6.2.2 Study Drug Discontinuation

If study drug administration is discontinued, the reason for discontinuation will be recorded.

6.3 Details of Procedures

6.3.1 Study Materials

Bristol-Myers Squibb (BMS) will provide ipilimumab at no cost for this study.

6.3.2 Safety Assessments

All patients who receive at least one dose of ipilimumab will be considered evaluable for safety parameters. Additionally, any occurrence of a SAE from time of consent forward, up to and including follow-up visits will be reported. See Section 8: Adverse Event Reporting.

Safety will be evaluated for all treated patients using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (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.

6.4 Criteria for Evaluation

6.4.1 Safety Evaluation

Refer to the NCI CTCAE, Version 4.0 (http://ctep.cancer.gov). SAEs will be assessed every three weeks during the first four cycles of ipilimumab and every 12 weeks during the fifth through eighth cycle of ipilimumab.

6.4.2 Efficacy Evaluation

The **primary endpoint** is fraction of patients who achieve an undetectable PSA (≤ 0.2 ng/ml). Pursuant to that endpoint, we will check the PSA every 3 weeks during the first 4 cycles and every 6 weeks during weeks 12-24, then every three months as the patient is being followed (planned follow up through year 5).

The **secondary endpoints** explore the objective responses achieved in the realm of non-progression of disease and tumor regression, as well as provide an opportunity to learn more about the immune response itself. Part of this assessment is PSA-based and part is based on radiographs (bone scans and CT scans). We will use the procedures described for the primary endpoint, above, to look at response endpoints. Additionally, a CT scan of the chest/abdomen/pelvis and bone scan at baseline, week 12, week 24 and every 6 months thereafter will be done for comparison. We will also perform a history and physical prior each cycle to detect new pain that could indicate cancer progression. After the 8 cycles of ipilimumab, patients will have their PSA checked every 3 months, either at the study center or by an outside provider. Their survival status will be assessed by telephone survey every 6 months for a maximum of 5 years. For the correlative work, we will collect blood samples prior to each infusion of ipilimumab and quantify the immune response. Once the study is complete, we will compare the objective response with the depth of the immune response.

6.4.2.1 Definitions of PSA-Related Secondary Endpoints

PSA progression: PSA increase of ≥ 25% and at least 2 ng/mL from baseline or nadir PSA achieved, confirmed by a second measurement at least three weeks later.

PSA nadir: Lowest PSA reached that was confirmed by a second equal or lower measurement.

PSA response: As recommended by the PCWG2 definitions. We will not apply a strict definition for PSA response. The primary endpoint is the proportion of patients with a PSA < 0.2 ng/ml on this study. Waterfall plots will be used to describe PSA changes while on study.

Maximum percentage of PSA reduction in each patient. Percentage of PSA reduction will be defined as [1 - (lowest PSA attained on study)/(PSA at study entry)] x 100. This formula only applies to PSAs that have decreased, and not those that have remained constant, i.e. the same as the baseline measurement.

6.4.2.2 Definition of Measurable and Non-Measurable Lesions

The guidelines contained here are based on recommendations of the Prostate Cancer Clinical Trials Working Group's 2007 definitions (PCWG2).[28]

The PCWG2 definitions use modified RECIST criteria.

Measurable lesions are visceral or extranodal lesions that are ≥ 1 cm in one direction. Lymph nodes are measurable lesions if they are ≥ 2 cm in one direction. Tumor in the prostate may also be used as a measurable lesion.

Non-measurable lesions are those lesions that do not meet the size criteria given above. Other non-measurable lesions are cysts, leptomeningeal disease, ascites, pleural/pericardial effusions and lymphangitis cutis/pulmonis.

Bone lesions will not be considered measurable lesions.

All measurable and non-measurable lesions should be measured at Screening and at the defined tumor assessment time points. Extra assessments may be performed, as clinically indicated, if there is a suspicion of progression.

6.4.2.2 Definition of Index/Non-Index Lesions

All measurable lesions, up to a maximum of **five lesions per organ** and **ten lesions in total,** should be identified as *index* lesions to be measured and recorded on the medical record at Screening. The *index* lesions should be representative of all involved organs. In addition, *index* lesions should be selected based on their size (lesions with the longest diameters), their suitability for accurate repeat assessment by imaging techniques, and how representative they are of the patient's tumor burden. At Screening, a sum of the longest diameters for all *index* lesions will be calculated and considered the baseline sum of the longest diameters. Response criteria to be followed are listed below. The baseline sum will be used as the reference point to determine the objective tumor response of the *index* lesions at tumor assessment (TA).

Measurable lesions, other than *index* lesions, and all sites of non-measurable disease, will be identified as *non-index* lesions. *Non-index* lesions will be recorded on the medical record and should be evaluated at the same assessment time points as the *index* lesions. In subsequent assessments, *non-index* lesions will be recorded as "stable or decreased disease", "absent", or "progression".

6.4.3 Evaluation of Tumor Response Using mRECIST Criteria

6.4.3.1 Definition of Index Lesion Response Using mRECIST

* Complete Response (CR):	Disappearance of all target lesions
* Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
* Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

6.4.3.2 Definition of Non -Index Lesion Response Using mRECIST

* Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. Must be confirmed by a scan done within 4-12 weeks after the first scan.
* Incomplete Response/Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
* Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions*

*Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

Evaluation of Bone Lesions:

For bone lesions, a minimum of two new lesions must be seen on bone scan to be determined progression of disease. Any lesion on bone scan suspected to be flare or inflammation, another study (such as CT or MRI scan) should be done to document the

presence of a new lesion. Bone scan interpretation will follow PCWG2 recommendations.

6.4.3.3 Determination of Overall Response Using mRECIST

Overall Response (OR) is determined as the combination of assessments of *index* and *non-index* lesions using the following criteria:

Index Lesion Assessment	*Non-Index Lesion Assessment*	*New Lesions*	***Overall Response***
CR	CR	No	**CR**
CR	SD	No	**PR**
PR	CR or SD	No	**PR**
SD	CR or SD	No	**SD**
PD	Any	Yes or No	**PD**
Any	PD	Yes or No	**PD**
Any	**Any**	**Yes**	**PD**

Best OR is the best confirmed response designation over the study as a whole, recorded between the date of first dose until the last tumor assessment for the individual patient in the study. The assessment of response will be at 6 months or sooner if progression is suspected. For the assessment of best OR, all available assessments per patient are considered. **CR or PR determinations included in the best OR assessment must be confirmed by a second (confirmatory) evaluation meeting the criteria for response and performed no less than 4 weeks after the criteria for response are first met**. It may be done between 4 and 12 weeks after the first scan that showed a response.

Imaging of the chest, abdomen and pelvis is required at screening (i.e., baseline) and at each tumor assessment visit, regardless of the location of known metastases. Specifically, a CT scan of the chest, abdomen and pelvis will be done at baseline, 12 weeks, and every 12 weeks while on the study. Similar methods of tumor assessment and similar techniques must be used to characterize each identified and reported lesion at screening

and during subsequent tumor assessments. Imaging-based evaluation is preferred to clinical examination.

If progressive disease is assessed based only on a new lesion(s) found on bone scans, additional imaging studies of the lesion(s) should be performed to confirm the malignant nature of the new findings on the bone scan. 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. New areas of abnormal uptake on a bone scan represent progressive disease.

6.4.4 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 may have objective increase of tumor lesions or other disease parameters (based on study indication, i.e., hematologic malignancies) within 12 weeks following start of ipilimumab dosing. Such patients may not have had sufficient time to develop the required immune activation or, in some patients, apparent mRECIST progression may represent infiltration of lymphocytes into the original tumor or blood. In conventional studies, such apparent radiographic progression or relevant laboratory parameter increases during the first 12 weeks of the study would constitute PD and lead to discontinuation of imaging to detect response, thus disregarding the potential for subsequent immune-mediated clinical response. In this study, it may not represent actual tumor progression.

Therefore, patients with tumor progression detected or lack of laboratory parameter response documentation prior to week 12 but without rapid clinical deterioration should continue to be treated with ipilimumab and clinically observed with a stringent imaging schedule to allow detection of a subsequent tumor response. This will improve the overall assessment of the clinical activity or ipilimumab and more likely capture its true potential to induce clinical responses. Investigational Product: IPILIMUMAB

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

Other medications used in the study as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, are considered non-investigational products. In this protocol, there are no non-investigational product(s).

Identification

Ipilimumab is available in 5 mg/mL single-use vials (10 mL or 40 mL). The sterile solution in the vial is clear and colorless. Ipilimumab is administered via intravenous infusion only.

6.5 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. Ipilimumab will be supplied at a concentration of 5 mg/mL in vials containing 10 ml or 40 mL solution.

6.6 Storage, Handling, and Dispensing

6.6.1 Storage

Ipilimumab must be stored in a secure area according to local regulations. The investigator must ensure that it is stored in accordance with the environmental conditions as determined by BMS and defined in the Investigator Brochure or SmPC/reference label. Ipilimumab must be stored at a temperature ≥ 2°C and ≤ 8°C.

6.6.2 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.

6.6.3 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.

6.7 Drug Ordering and Accountability

6.7.1 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 marianne.simone@bms.com and dsc.wfd@bms.com. Please fax to (203) 677-6489 (U.S.) if you cannot send the form electronically.

Ipilimumab vials (10 mL and 40 mL) are shipped in quantities of ten. Allow 5 business days for shipment of drug from BMS receipt of the ipilimumab Clinical Supply Shipment 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 BMS 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.

6.7.2 Re-Supply

Reorders should be emailed directly to BMS using marianne.simone@bms.com and dsc.wfd@bms.com 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.

6.8 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.

6.9 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.

7 ADVERSE EVENT REPORTING

7.1 Collection of Safety Information

The OHSU IRB defines an Unanticipated Problem (UP) as an event that is not expected given the nature of the research procedures and the patient population being studied and suggests that the research places patients or others at a greater risk of harm or discomfort related to the research than was previously known or recognized. Harm to a patient need not occur for an event to be a UP.

Reportable Adverse Event – AEs which qualify as unanticipated problems that must be reported by the PI to the IRB and by the IRB to the Institutional Official and to OHRP are categorized as follows:

- On Protocol Serious Adverse Events (SAEs) that are unexpected and related or possibly related to participation in the research.
- On Protocol SAEs or AEs that are expected in some patients, are related or possibly related, but are determined to be occurring at a significantly higher frequency or severity than expected.
- On or Off Protocol Unexpected SAEs or AEs that are related or possibly related, regardless of severity, that may alter the IRB's analysis of the risk versus potential benefit of the research and, as a result, warrant consideration of substantive changes in the research protocol or informed consent process/document.

Other events that are On or Off Protocol and unexpected that may place patients or others at a greater risk of harm or discomfort than was previously known or recognized. Harm to a patient need not have occurred.

All Reportable Adverse Events, as defined in this section occurring after patient enrollment must be reported to the Principal Investigator, Dr. Julie Graff at 503.220.8262, extension 55688, or graffj@ohsu.edu. The Principal Investigator has the obligation to report all serious adverse experiences to the FDA, OHSU IRB, Bristol-Myers Squibb, and other participating sites in accordance with the following guidelines.

7.1.1 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
- 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 [eg, 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 not 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 (eg, 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 (eg, 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.

7.1.2 Nonserious Adverse Events

All adverse events that are not classified as serious.

7.2 Assignment of Adverse Event Intensity and Relationship to Investigational Product

All adverse events, including those that are serious, will be graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE), Version 4.0.

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

- Certain: There is a reasonable causal relationship between the investigational product and the AE. The event responds to withdrawal of investigational product (dechallenge), and recurs with rechallenge when clinically feasible.
- Probable: There is a reasonable causal relationship between the investigational product and the AE. The event responds to dechallenge. Rechallenge is not required.
- Possible: There is reasonable causal relationship between the investigational product and the AE. Dechallenge information is lacking or unclear.
- Not likely: There is a temporal relationship to investigational product administration, but there is not a reasonable causal relationship between the investigational product and the AE.
- Not Related: There is not a temporal relationship to investigational product administration (too early, or late, or investigational product not taken), or there is a reasonable causal relationship between noninvestigational product, concurrent disease, or circumstance and the AE.

The expression "reasonable causal relationship" is meant to convey in general that there are facts (eg, evidence such as de-challenge/re-challenge) or other arguments to suggest a positive causal relationship.

7.3 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.

7.3.1 Serious Adverse Events

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 (eg, a follow-up skin biopsy). The investigator should notify

BMS of any SAE occurring after this time period that is believed to be certainly, probably, or possibly related to the investigational product or protocol-specified procedure.

All SAEs whether related or unrelated to the ipilimumab, must be immediately reported to BMS (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.

Participating centers will notify the Lead Site, OHSU, of all SAEs within 24 hours of becoming aware of the event. Reporting will occur by MedWatch Form 3500A with supporting documentation. OHSU will report this information to BMS and/or the FDA, as appropriate.

All SAEs should be faxed or emailed to BMS at:

Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
Fax Number: 609-818-3804
Email: Worldwide.safety@bms.com

For studies conducted under an Investigator IND, any event that is both serious and unexpected must be reported to the FDA as soon as possible and, in no event, later than 7 days (death or life-threatening event) or 15 days (all other SAEs) after the investigator's or institution's initial receipt of the information. BMS will be provided with a simultaneous copy of all adverse events filed with the FDA. 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
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178 (1-800-332-0178)
http://www.accessdata.fda.gov/scripts/medwatch/

All SAEs should simultaneously be faxed or e-mailed to BMS at:

Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
Fax Number: 609-818-3804
Email: Worldwide.safety@bms.com

Serious adverse events, whether related or unrelated to investigational product, must be recorded on the SAE page and reported expeditiously to BMS (or designee) to comply with regulatory requirements. An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

All SAEs must be immediately reported by confirmed facsimile transmission (fax) and mailing of the completed SAE page. In some instances where a facsimile machine is not available, overnight express mail may be used. If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.) In selected circumstances, the protocol may specify conditions that require additional telephone reporting.

If the investigator believes that an SAE is not related to the investigational product, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE page.

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 Handling of Expedited Safety Reports

In accordance with local regulations, BMS will notify investigators of all SAEs that are suspected (certainly, probably, or possibly related to the investigational product) and unexpected (ie, not previously described in the Investigator Brochure). In the European Union (EU), an event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). 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 (eg, 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.

In addition, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

7.3.3 Nonserious Adverse Events

The collection of nonserious AE information should begin at initiation of investigational product. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

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

All identified nonserious AEs must be recorded and described in the medical record.

7.3.4 Pregnancy

All participants will be male. If a female partner becomes pregnant during the research study, the female partner will be asked to sign a consent to follow the pregnancy for outcomes and any possible side effects from the study drug.

7.3.5 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded in the medical record.

8 STATISTICAL METHODOLOGY

8.1 Study Design

This is a single arm phase II trial.

8.2 Primary and Secondary Endpoints

The primary endpoint is the achievement of an undetectable PSA defined as PSA ≤ 0.2 ng/mg after initiation of ipilimumab therapy. The secondary endpoints are: time to PSA progression, time to disease progression by any measure, time to death from any cause, number of patients with immune related Adverse Events (IRAEs), correlation between IRAEs and clinical outcomes, and the ratio of T regulatory cells to T effector cells, and additional measures of immune responses.

8.3 Sample Size Justification

N=30 (for the final analysis, 10 for the intial analysis). Using the Simon two-stage design for Phase II trials, the initial accrual will be 10 patients. Assuming that 10% of patients receiving usual care will achieve an undetectable PSA (PSA ≤ 0.2) without additional intervention, the trial has a 80% power to detect a rate of achieving an undetectable PSA of ≥ 30% among patients treated with ipilimumab. At least two patients with an undetectable PSA will be required in the first 10 patients to continue to stage 2. As soon as two patients having achieved an undectable PSA are identified, stage 2 for of the study will begin. If 6 or more of 30 patients have achieved an undetectable PSA at 6 months, the study will be considered successful and the regimen worthy of further investigation. This design has a type I error rate of 0.05 and a type II error rate of 0.20.

8.4 Analysis Populations

An Intention to Treat (ITT) population includes all patients who sign the consent and are assigned to a treatment regardless of the actual drug dose the patients receive. Safety analysis population includes all patients who receive at least one drug dose. Per Protocol

Population includes those who receive the prescribed dose of the drug per protocol and excludes patients who drop out of the study prematurely. Whenever possible, we will use the ITT population to analyze the primary and secondary endpoints provided that their primary and secondary endpoints are measured. As a secondary analysis, per protocol population will be used for the analysis of the primary and secondary endpoints. Safety analysis population will be used to analyze safety and toxicity data.

8.5 Statistical Analysis Plan

Demographic and clinical characteristics will be summarized using descriptive statistics (e.g. proportions, mean, standard deviation, median, range). The proportion of patients who achieve an undetectable PSA (≤ 0.2 ng/ml) after initiation of ipilimumab therapy will be provided with the exact 95% confidence interval. The Kaplan-Meier method will be used to estimate time to PSA progression, time to disease progression by any measure and time to death from any cause. In evaluation of time to PSA progression and time to disease progression by any measure will be censored for:

1) lost to follow-up at the date of last contact
2) use of additional cancer therapies that would interfere with ascertainment of the endpoint of interest
3) death from a causes other than prostate cancer or treatment of prostate cancer.

Evaluation of time to death will be censored for lost to follow-up at last contact.

The effects of IRAEs and other immune parameters (e.g., a ratio of T regulatory cells to T effector cells) on clinical outcomes will be evaluated using logistic regression for binary endpoints (e.g., achievement of undetectable PSA) and Cox regression for the time to event outcomes (e.g., time to PSA progression).

8.6 Safety Analysis

All toxicity and safety data including immune related Adverse Events (IRAEs) will be tabulated for each treatment group and summarized according to major organ categories of the NCI CTCAE v 4.0.

8.7 Efficacy Analysis

See section 9.5

9 ADMINISTRATIVE SECTION

9.1 Compliance with the Protocol and Protocol Revisions

The protocol and informed consent form for this study must be reviewed and approved in writing by the OHSU Knight Cancer Institute Clinical Research Review Committee (CRRC) and Institutional Review Board (IRB) at OHSU prior to any patient being registered on this study at OHSU. In addition, the protocol and informed consent must be reviewed by the IRB of each institution participating in this Prostate Cancer Clinical Trials Consortium (PCCTC) study before any patients may be registered from those individual institutions.

Any modification of this protocol must be documented in the form of a protocol revision or amendment signed by the principal investigator and approved by the OHSU CRRC and OHSU IRB, before the revision or amendment may be implemented. The only circumstance in which the amendment may be initiated without regulatory approval is for a change necessary to eliminate an apparent and immediate hazard to the patient. In that event, the investigator must notify the CRRC and IRB in writing within 10 working days after the implementation. Investigators holding the IND must notify FDA of substantive changes to the protocol.

9.2 Informed Consent

Investigators must ensure that subjects, or, in those situations where consent cannot be given by subjects, their legally acceptable representative, are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate. Freely given written informed consent must be obtained from every subject or, in those situations where consent cannot be given by subjects, their legally acceptable representative, prior to clinical study participation, including informed consent for any screening procedures conducted to establish subject eligibility for the study.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

9.3 Records and Reports

If the investigator relocates or for any reason withdraws from the study, the study records must be transferred to an agreed upon designee, such as another institution, another investigator, or to the OHSU Knight Cancer Institute Clinical Research Management. Records must be maintained according to sponsor or FDA requirements.

9.4 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.

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

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects. The investigator should also provide the IRB/IEC with a copy of the

Investigator Brochure or product labeling, information to be provided to subjects and any updates.

The investigator should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures

9.6 Records Retention

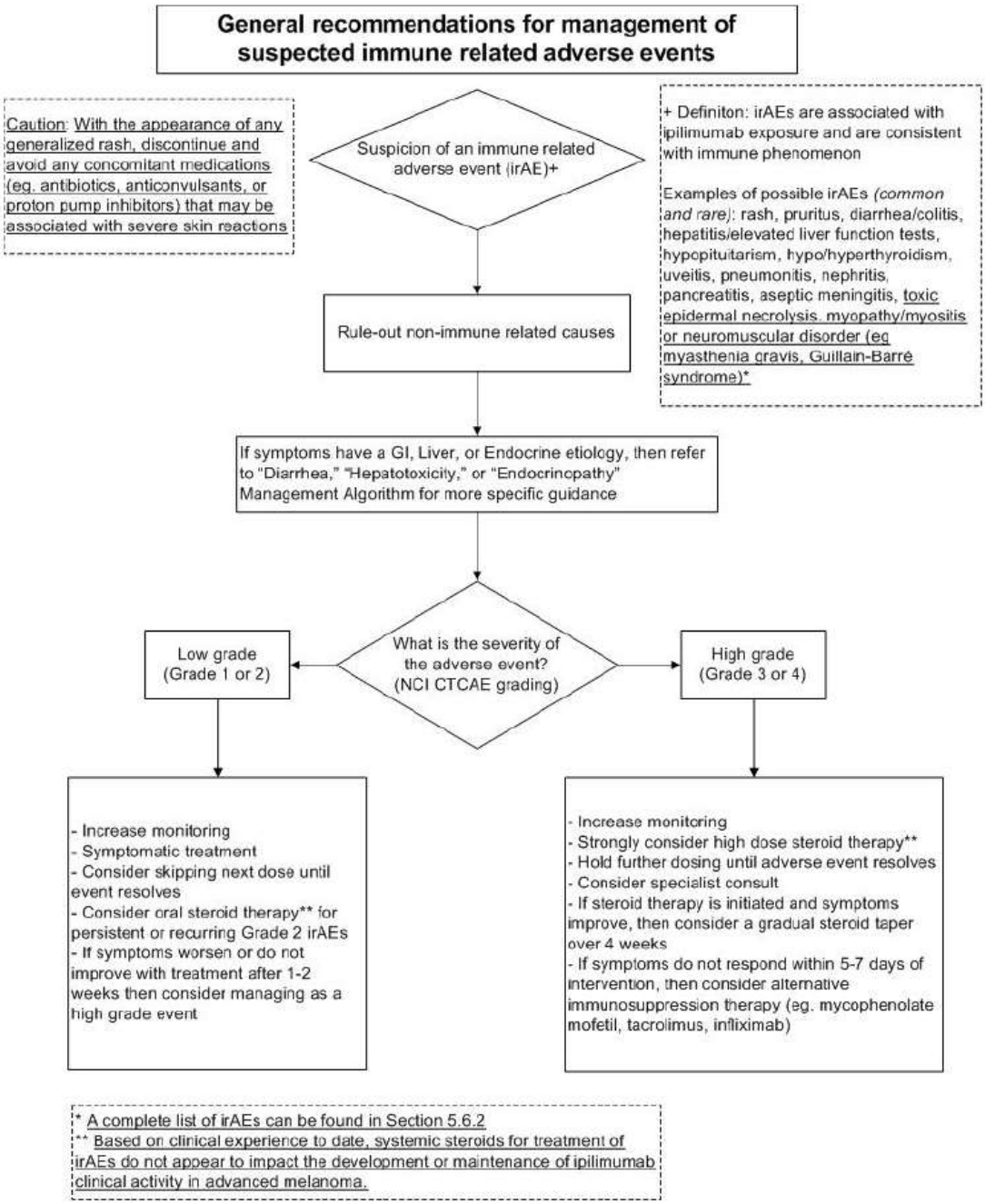
The Investigator must retain Ipilimumab disposition records, source documents, and case histories designed to record all observations and other data pertinent to the investigation (e.g. case report form) for the maximum period required by applicable regulations and guidelines, or Institution procedures.

If the Investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another Investigator, IRB). Documentation of such transfer must be provided to BMS.

APPENDIX 1 LIST OF ABBREVIATIONS

Abbreviation	Term
ANC	Absolute Neutrophil Count
AST	Androgen Suppression Therapy
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
PCWG2	Prostate Cancer Working Group 2
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
SPD	Sum of the products diameters
SD	Stable Disease
TNM Staging	Tumor, Node and Metastasis Staging
TA	Tumor assessment

APPENDIX 2 GENERAL RECOMMENDATIONS FOR IMMUNE-RELATED ADVERSE EVENTS (IRAES)



APPENDIX 3 SUGGESTED WORK-UP AND TREATMENT FOR IMMUNE-RELATED ADVERSE EVENTS (IRAES)

An IRAE is defined as an adverse event of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event a non-dermatologic, immune-mediated event. Serological, immunological, and histological (biopsy) data should be used to support the diagnosis of an immune-mediated toxicity. Documentation of test results should be included in the patient's medical record.

Gastrointestinal (diarrhea) and skin (rash)-related toxicities have been the most common IRAEs noted in prior studies with ipilimumab. Suggested work-up procedures for suspected IRAEs of the gastrointestinal tract, liver, skin, eye, pituitary, and adrenal gland are listed below. When symptomatic therapy is inadequate or inappropriate, an IRAE should be treated with steroids followed by a slow taper.

Gastrointestinal Tract: Diarrhea (defined as either first watery stool, or increase in frequency 50% above baseline with urgency or nocturnal bowel movement, or bloody stool) should be further evaluated and infectious or alternate etiologies ruled out. Patients should be advised to inform the investigator if any diarrhea occurs, even if it is mild. An algorithm for working up patients with diarrhea or suspected colitis is provided in Appendix 4.

If the event is of significant duration or magnitude or is associated with signs of systemic inflammation or acute phase reactants (e.g., increased CRP or platelet count; or bandemia), it is recommended that sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy with 3 to 5 specimens for standard paraffin block be performed. If possible, 1 to 2 biopsy specimens should be snap frozen and stored. All patients with confirmed colitis should also have an opthomological examination, including a slit-lamp exam, to rule out uveitis. Tests should also be performed for WBCs and for stool calprotectin.

Patients with colitis should discontinue any non-steroidal anti-inflammatory medications or any other medications known to exacerbate colitis symptoms. Investigators should use their clinical judgment as to whether corticosteroids are necessary to treat colitis associated with ipilimumab therapy and as to what dose should be used. As guidance prior experience suggests that colitis manifested as ≥ Grade 3 diarrhea requires

corticosteroid treatment. For severe symptoms, prednisone 60 mg or equivalent may be required to control initial symptoms and the dose should be gradually tapered over at least one month in duration. Lower doses of prednisone may be considered for less severe cases of colitis. It is suggested that prednisone (for oral administration) or solumedrol (for intravenous administration) be corticosteroid of choice in the treatment of colitis.

Liver: Elevation of LFTs ≥ 3 fold from baseline should instigate an investigation into the underlying etiology for suspected IRAEs. Neoplastic, concurrent medications, viral hepatitis, and toxic etiologies should be considered and addressed, as appropriate. Imaging of the liver, gall bladder, and bile duct should be performed to rule out neoplastic or other causes for the increased LFTs. An ANA, pANCA, and anti-smooth muscle antibody test should be performed if an autoimmune etiology is considered. Consultation with a hepatologist is appropriate for a suspected liver IRAE and a biopsy should be considered.

Patients presenting with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have LFTs performed immediately and reviewed before administering the next dose of study drug. Treating physicians should discuss, with the CRO Medical Monitor, unexplained increases in LFTs ≥ 3 fold from baseline prior to any additional study drug administration.

Pancreas: Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, may rarely be associated with anti-CTLA-4 monoclonal antibody administration. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include serum amylase and lipase tests.

Skin: A dermatologist should evaluate persistent and/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 IRAEs have been treated with symptomatic therapy (e.g., antihistamines). Topical or parenteral corticosteroids may be required for more severe symptoms.

Eye: An ophthalmologist should evaluate visual complaints with examination of the conjunctiva, anterior and posterior chambers and retina; visual field testing and an electroretinogram should also be performed. Patients with ipilimumab related uveitis or episcleritis have been treated with topical corticosteroid eye drops.

Endocrine: Patients with unexplained symptoms such as fatigue, myalgias, impotence, mental status changes, or constipation should be investigated for the presence of thyroid, pituitary or adrenal endocrinopathies. An endocrinologist should be consulted if an endocrinopathy is suspected. TSH and free T4 levels should be obtained to determine if thyroid abnormalities are present. TSH, prolactin and a morning cortisol level will help to differentiate primary adrenal insufficiency from primary pituitary insufficiency. Appropriate hormone replacement therapy should be instituted if an endocrinopathy is documented.

Suspected IRAEs should be documented in the patient's medical record.

APPENDIX 4 **DIARRHEA MANAGEMENT ALGORITHM**

GI Toxicity Management Algorithm

Severity of diarrhea/ colitis	Management	Follow-up
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue ipilimumab. **Opiates/narcotics mask symptoms of perforation! Infliximab should not be used in case of perforation/sepsis!**		
Grade 1 Diarrhea: < 4 stools/day over baseline; Colitis: asymptomatic	• Continue ipilimumab • Symptomatic treatment	• Close monitoring for worsening symptoms • Educate patient to report any worsening immediately
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated < 24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Withhold/delay ipilimumab • Symptomatic treatment	**Symptoms improve/resolve** (grade 0/1): Resume ipilimumab **Symptoms persist for > 5-7 days, worsen, or recur:** • Moderate to high dose steroids PO (e.g., prednisone 0.5 - 1 mg/kg/day) • Continue to hold/delay ipilimumab until grade 1 • When symptoms are grade 1 or less slowly taper steroids over at least 1 month and resume ipilimumab. **Symptoms worsen:** Treat as grade 3/4
Grade 3-4 Diarrhea (G3*): ≥ 7 stools per day over baseline; incontinence; IV fluids ≥ 24 hrs;interfering with ADL Colitis (G3*): fever, ileus, peritoneal signs	• Permanently discontinue ipilimumab • High dose IV steroids (e.g., methylprednisolone 1-2 mg/kg/day) • Consider endoscopy	**Symptoms improve:** • Continue steroids (same dose) until grade 1 • Then taper over at least 1 month **Symptoms persist 3-5 days, or recur after improvement:** • 1 dose* of infliximab 5 mg/kg (if no contraindication)
*G4 = life-threatening, perforation		*Some patients have required a second dose of infliximab

Patients on IV steroids may be switched to oral corticosteroid (e.g., prednisone) at an equivalent dose 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 the equivalent dose of PO corticosteroids.

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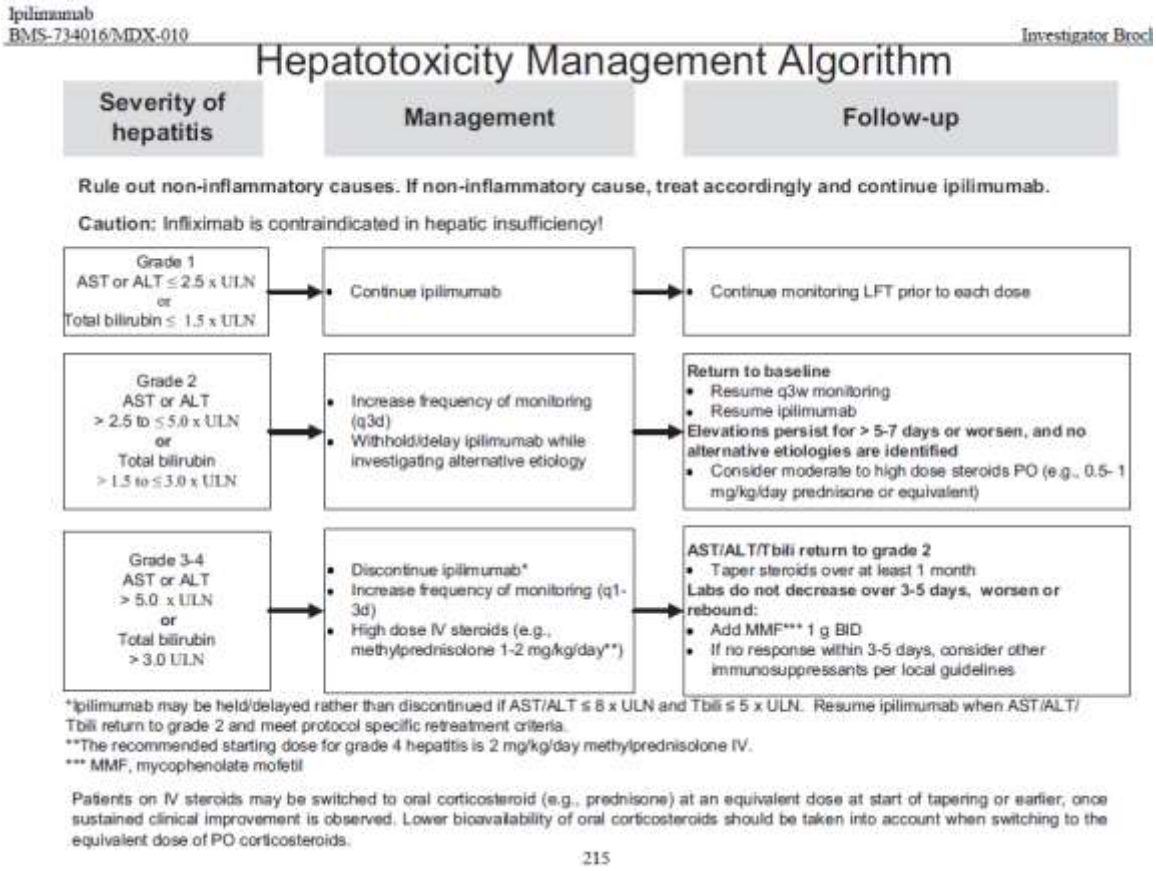
GRADE 1	**GRADE 2**	**GRADE 3**	**GRADE 4**	**GRADE 5**
Increase of < 4 stools per day over baseline; mild increase in ostomy output compared with baseline	Increase of 4-6 stools per day over baseline; IV fluids indicated < 24 hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL	Increase of ≥ 7 stools per day over baseline; incontinence; IV fluids ≥ 24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL	Life-threatening consequences (eg, hemodynamic collapse)	Death

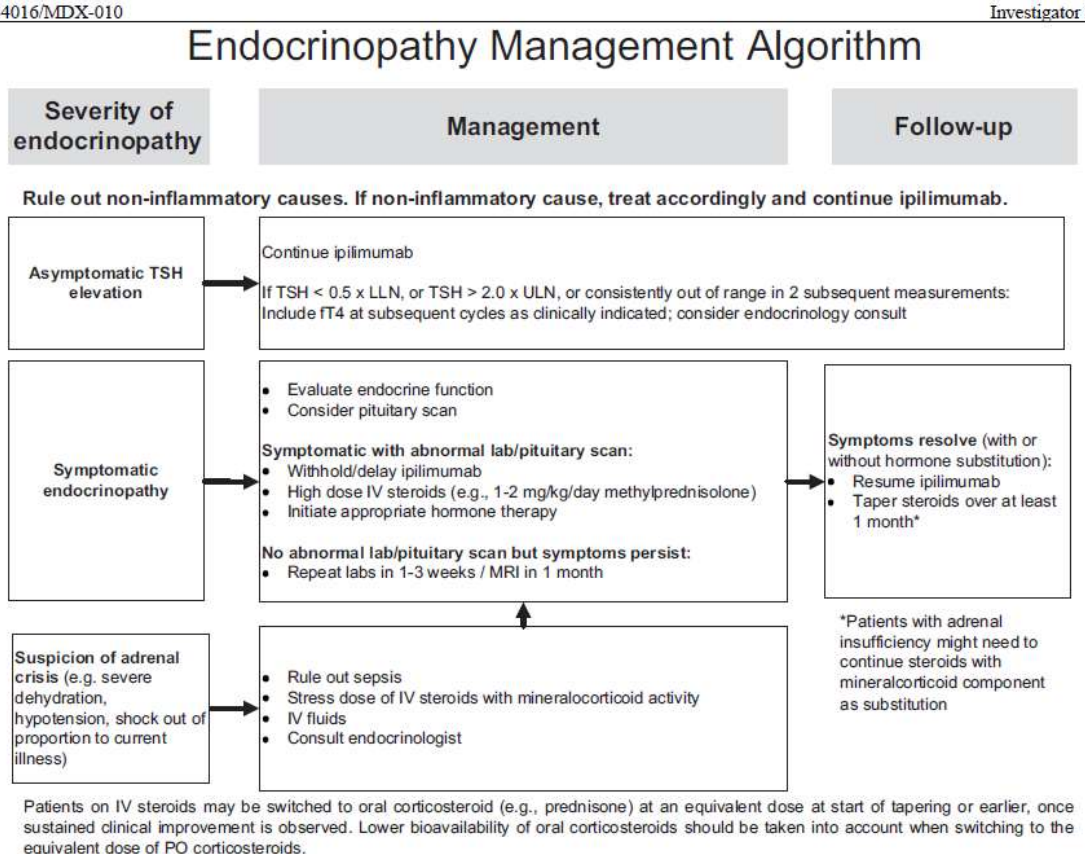
APPENDIX 5 HEPATOTOXICITY MANAGEMENT ALGORITHM

The most current experience with immune-related hepatitis has allowed further development of this management algorithm to include recommendations for treatment.

HEPATOTOXICITY THERAPEUTIC INTERVENTION ALGORITHM



APPENDIX 6 **ENDOCRINOPATHY MANAGEMENT ALGORITHM**



APPENDIX 7 SAMPLE COLLECTION/HANDLING AND SHIPPING

Correlative studies will be drawn just prior to administration of ipilimumab doses 1 through 4. After drawing the samples, the tubes should be processed as soon as possible, ideally within 1 hour of the blood draw. (It is recommended that the serum aliquots be frozen and whole blood be refrigerated within 2 hours of processing.)

1) Collect 10mL of blood into each of the six tubes: 5 green top (heparin), 1 red top. All tubes to be obtained from a local vendor.

GREEN TOP TUBE INSTRUCTIONS:

2) Invert the green top tubes several times to mix well and put them on ice.
3) Store the investigational samples in an upright position at 4°C until ready for shipping.
4) When ready for shipping, put the tubes in a plastic biohazard bag (obtained from a local vendor) and seal the bag. Please ship specimens in a Styrofoam shipping container (obtained from a local vendor). Place enough cold packs at 4-24°C (obtained from a local vendor) to cover the bottom of the Styrofoam container.

RED TOP TUBE INSTRUCTIONS:

5) Centrifuge the red top tube at 3000 rpm for 10-15 minutes.
6) Using a polyethylene transfer pipette, draw off the serum and transfer it into 1 mL Cryovials. Use 2 Cryovials for serum. Cap and label the Cryovial with Patient Study Number, date and time point (i.e. Screening, Cycle X, or off study).
7) Freeze and store the Investigational samples in an upright position at -80°C until shipped to OHSU on dry ice.
8) When ready for shipping, place the samples in a plastic biohazard bag and seal the bag. Cover the bottom of a separate (not from step 4) Styrofoam container with dry ice. Place the biohazard bag containing the samples on the dry ice and cover with 7 to 10 pounds of additional dry ice.

SHIPPING INSTRUCTIONS:

9) Shipments can be sent Monday through Thursday, via overnight delivery. (DO NOT SHIP SAMPLES ON FRIDAY.) Please notify the receiving Study Coordinator of incoming samples by phone or email prior to shipment. Ship to the address below.

DERRICK DOMANN-SCHOLZ , OREGON HEALTH & SCIENCE UNIVERSITY
3303 SW Bond Avenue, CH14R
CHH 14040
Portland, OR, 97239
PHONE: (503) 494-6179
FAX: (503) 494-6197
EMAIL: domannsc@ohsu.edu

OHSU will batch and ship the samples to be analyzed at theUniversity of California San Francisco.

APPENDIX 8: ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

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