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Title: A Phase II Single Arm Study of High-Dose IL-2 and Ipilimumab in Patients with Unresectable Stage III and Stage IV Melanoma

Principal Investigator: [redacted]

[redacted]

Supported by: [redacted]

Drug(s) Under Investigation:

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CONFIDENTIAL

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Designated Comprehensive Cancer Center

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CLINICAL PROTOCOL *CA184-084*

A Phase II Single Arm Study of High-Dose IL-2 and Ipilimumab in Patients with Unresectable Stage III and Stage IV Melanoma

Principal Investigator and Coordinating Center:

[redacted]

Protocol Amendment 4.0 / *11 August 2016*

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PROTOCOL SYNOPSIS

Protocol Title:	A Phase II Single Arm Study of High-Dose IL-2 and Ipilimumab in Patients with Unresectable Stage III and Stage IV Melanoma
Site Names:	[redacted]
Research Hypotheses:	1. The combination of Ipilimumab and high-dose IL-2 improves clinical responses. 2. The combination of Ipilimumab and high-dose IL-2 is feasible and has an acceptable safety profile. 3. The combination of Ipilimumab and high-dose IL-2 results in increased effector CD8+ T cells and decreased CD4+FoxP3+ regulatory T cells in responding patients.
Study Schema: **Drugs / Doses / Length of Treatment)**	**Ipilimumab (Yervoy)** Each patient will receive ipilimumab 10 mg/kg by intravenous (IV) infusion over 90 minutes (not bolus or IV push). Yervoy is approved for the treatment of metastatic melanoma by the U.S. FDA. **Interleukin-2 (Aldesleukin)** Each patient will receive IL-2 given intravenously (IV) in a dose of 600,000 IU/kg every eight hours for up to 14 doses in each cycle according to institutional guidelines. Aldesleukin is approved for the treatment of metastatic melanoma by the U.S. FDA. Patients will be enrolled as follows: **Study Design:** Ipilimumab (10 mg/kg) for 4cycles (Days 1, 22, 43, 64) and high-dose IL-2 for 2 cycles (Days 22-26, 43-47). At week 24, maintenance Ipilimumab will be given and at 3 month intervals for 4 doses. **Length of Treatment**: The total treatment period is 15 months and follow-up will continue for a total of 36 months Study Design Induction: Ipilimumab (10 mg/kg) for 4 doses (Days 1, 22, 43, 64) and high-dose IL-2 for 2 cycles (Days 22-26, 43-47). Maintenance Ipilimumab: At week 24, maintenance Ipilimumab will be given and at 3 month intervals for 4 doses. Long Term Survival Follow-up: Will be conducted by phone every 6 months.

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Study Objectives: **Primary:** **Secondary:**	**Primary Endpoint:** 1. The best overall response rate at or before week 24 of treatment per modified WHO response criteria. **Secondary Clinical Endpoints**: 1. Safety and feasibility 2. Progression-free survival 3. Overall survival 4. Survival rate at 1, 2 and 3 years 5. Best overall response rate 6. Disease control rate (CR+PR+SD) **Secondary Immune Endpoints:** 1.Frequency of effector CD8+ T cells 2.Frequency of CD4+FoxP3+ regulatory T cells
Study Design:	Eligible patients will be enrolled in an open-label, single arm trial employing standard high-dose IL-2 (600,000 I.U./kg i.v. every 8 hours to 14 maximum doses) and ipilimumab (10 mg/kg i.v. infusion over 90 minutes) as follows: Ipilimumab (10 mg/kg) for 4 cycles (Days 1, 22, 43, 64) and high-dose IL-2 (600,000 IU/kg every 8 hours to 14 total doses as tolerated) for 2 cycles (Days 22-26, 43-47). Beginning on week 24, patients who do not have disease progression or unacceptable toxicity will receive maintenance ipilimumab (10 mg/kg) IV over 90 minutes. Treatment repeats every 90 days for a maximum of 4 courses in the absence of disease progression or unacceptable toxicity. Once maintenance ipilimumab is completed patients will go into long term survival follow up. Patients will be followed for up to 36 months from study enrollment for survival analysis. Ipilimumab will be provided by BMS.
Accrual Goal: **(Total number of patients)**	A total of 82 patients will be enrolled.
Accrual Rate: **(Number of patients expected per month)**	10 / month with the expectation that accrual will be complete in 12 months and follow-up will be complete at 48 months.
FPFV: **LPFV:** **Follow Up:** **(dd-mm-yy)**	09-10-14 – 09-10-15 09-10-15 – 09-10-16 Follow-Up Complete 09-10-18

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Correlative Studies: (PK/PD, etc.)	Immune studies at screening and week 1 (baseline) and at weeks, 4 , 7, and 12 and at 6 and 12 months (CD8+ T cells, Tregs)
Inclusion Criteria:	An individual must meet all the following criteria: 1) Willing and able to give written informed consent. 2) Histologic or cytologic diagnosis of cutaneous melanoma that is considered unresectable (Stage III) or metastatic (Stage IV). Ocular and mucosal melanoma is excluded. 3) Required values for initial laboratory tests: · WBC ≥ 2000/uL · ANC ≥ 1000/uL · Platelets ≥ 75 x 10^3/uL · Hemoglobin ≥ 9 g/dL (≥ 80 g/L; may be transfused) · Creatinine ≤ 2.0 x ULN · AST/ALT ≤ 2.5 x ULN for patients without liver metastasis, ≤ 5 times for patients with liver metastases · Total Bilirubin ≤ 2.0 x ULN, (except patients with Gilbert's Syndrome, who must have a total bilirubin less than 3.0 mg/dL) 4) No known active or chronic infection with HIV, Hepatitis B, or Hepatitis C. Testing is not required unless clinically suspected. 5) Performance status (ECOG 0-1). 6) Patients must have a life expectancy of greater than three months at the start of the trial. 7) Patients must have a brain MRI that is free of active metastases. Metastases that have been treated with radiation or surgical resection, are stable for at least 4 weeks and do not require steroids are eligible. 8) Patients may have received treatment of completely resected early stage melanoma, comprising interferon, radiation treatment, or experimental vaccine therapy, and in the metastatic setting patient can have had treatment such as chemotherapy, immunotherapy (except prior treatment with Ipilimumab and IL-2), and other experimental agent which was completed 4 weeks prior to enrollment. 9) Normal cardiac stress test for patients over 50 years of age. 10) Pulmonary Function: FEV1 and FVC > 65% of prediction for those patients with extensive pulmonary metastases or chronic pulmonary disease history. *11)* Men and women, ≥ 18 years of age.

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Exclusion Criteria:	1. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit study compliance 2. Any other malignancy form which the patient has been disease-free for less than 5 years, with the exception of adequately treated and cured basal or squamous cell skin cancer, superficial bladder cancer or carcinoma in situ of the cervix. 3. Patients with primary ocular or mucosal melanoma are excluded. 4. Autoimmune disease: Patients with a history of inflammatory bowel disease, including ulcerative colitis and Crohn's Diseasse, are excluded from this study, as are patients with a history of symptomatic disease (e.g., rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, autoimmune vasculitis [eg, Wegener's Granulomatosis]); motor neuropathy considered of autoimmune origin (e.g. Guillain-Barre Syndrome and Myasthenia Gravis). 5. 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. 6. Patients with underlying heart conditions who are deemed ineligible for surgery by cardiology consult. Patients with reversible ischemic changes on cardiac stress test. 7. Any non-oncology vaccine therapy used for prevention of infectious diseases (for up to 1 month before or after any dose of ipilimumab). 8. A history of prior treatment with IL-2, ipilimumab or prior CTLA4 inhibitor or agonist for metastatic disease. Prior therapy with ipilimumab in the adjuvant setting is allowed provided there were no Grade 3 or greater adverse events that did not resolve with limited corticosteroid use; and more than 6 months have elapsed since final adjuvant treatment and start of study treatment on this protocol. 9. Concomitant therapy with any of the following: interferon, or other non-study immunotherapy regimens; cytotoxic chemotherapy; immunosuppressive agents; other investigation therapies; or chronic use of systemic corticosteroids. 10. Women of childbearing potential (WOCBP), defined above in Section 4.1, who: a.are unwilling or unable to use an acceptable method of contraception to avoid pregnancy for their entire study period and for at least 8 weeks after cessation of study drug, or b.have a positive pregnancy test at baseline, or c.are pregnant or breastfeeding. 11. Prisoners or subjects who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (eg, infectious) illness.

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Criteria for Evaluation: (Efficacy, safety, stopping rules, etc.)	1. Efficacy will be based on appropriate imaging studies (CT scan of the chest, abdomen and pelvis and MRI of the brain) at specified time points. PET scan will be done only for lesions that cannot be assessed by CT imaging. 2. Safety will be determined by NCI CTCAE, version 4.0. Criteria for stopping drug and patient withdrawal due to toxicity are detailed in Section 5.0 of the protocol. An interim safety analysis will be conducted after the first 6 patients are enrolled. An independent DSMB will review the safety data and if concerns are found the ipilimumab dose will be reduced to 3 mg/kg. 3. Standard stopping rules for Ipilimumab will be followed according to current practice guidelines; IL-2 doses will be held per standard practice guidelines; IL-2 will be stopped for standard stopping criteria and as detailed in Section 8 of the protocol.
Statistics:	Except where otherwise stated, descriptive statistics will be used. Continuous variables will be presented by summary statistics (such as mean, median, standard error and 90% CI and categorical variables by frequency distributions (i.e., frequency counts, percentages and 90% CI). The primary endpoint will be the best objective response at or before week 24 as determined by the modified WHO response criteria (mWHO). We will estimate the objective response rate as the ratio of the number of patients having best objective response over the total number of patients; this objective response rate will be compared with published response rate of Ipilimumab alone and IL-2 alone using exact one sample binomial tests. For sample size calculations, we assume that 14% of patients will respond to Ipilimumab alone and 17% (will respond to IL-2 alone. In order to see a significant clinical effect we will expect the combination to yield a response rate of at least 28% based on a previous Phase I trial. In order to have 80-% power at alpha=0.05 using a one sided one sample test under binomial distribution assumption to detect this difference, 82 evaluable patients will need to be enrolled and complete the initial treatment period. Secondary clinical and immune endpoints will be evaluated in an exploratory manner only using the following criteria: <u>Safety and toxicity</u> A secondary objective of this study is to determine the safety and toxicity of combination Ipilimumab and high-dose IL-2. The type, frequency and severity of unexpected adverse events will be noted in the intention-treat population. An interim safety analysis will be conducted after the first 6 patients are enrolled. An independent DSMB will review the safety data and if concerns are found the ipilimumab dose will be reduced to 3 mg/kg.

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Statistics (cont):	Toxicities will include abnormal hematology and biochemistry laboratories, which will be recorded at baseline and at various time points throughout the study. Adverse events will be listed by subjects within groups showing time of onset, period of event, grade classified using the CTCAE v.4.0, relationship to disease and outcome. The number of events in each classification of severity and relationship to treatment will be tabulated for each patient and summarized by treatment arm. Immunological Responses Evaluation of immunological responses will be primarily based on the breadth and magnitude of cellular responses. The frequency of effector CD8+ T cells and regulatory CD4+FoxP3+ Tregs will be measured pre-treatment and at various times post-treatment in the tumor (when feasible) and peripheral blood. Immune response for each patient will be measured as paired differences between pre and post measurements of these parameters at various times. Transformation of the data will be performed if appropriate, e.g. log transformation, and hence treatment effect will be expressed on a log scale. Clinical Response Objective clinical responses will be determined by immune-related response criteria (mWHO). Disease control rate (DCR) will include complete response, partial response and stable disease. Best overall response will also be recorded. Progression-free and Overall Survival will be assessed using Kaplan Meier plots using mWHO criteria. In addition, we will estimate and report the median survival as well as one year, two year and three year overall survival rates and their 90% confidence intervals.

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1. INTRODUCTION

1.1 Research Hypothesis

Melanoma is the most serious form of skin cancer and accounts for 80% of all skin cancer-related mortality. Despite considerable research efforts, the median survival for patients with metastatic melanoma is approximately 6-9 months. High-dose IL-2 induces objective clinical responses in 16-17% of patients and results in durable complete responses in 7-10% of melanoma patients. The mechanism of anti-tumor activity with high-dose IL-2 is not completely understood but recent data has suggested a correlation of therapeutic response with CD4+FoxP3+ regulatory T cell (Treg) frequency, pre-treatment serum biomarkers (e.g. VEGF, fibronectin) and host gene polymorphisms supporting a role for immune-mediated tumor rejection [1-3]. High-dose IL-2 (Proleukin) was approved for the treatment of metastatic melanoma by the FDA in 1998.

Cytotoxic T-lymphocyte associated protein (CTLA)-4 belongs to a negative homeostatic control mechanism regulating T cell activation. Preclinical studies of anti-CTLA-4 mAb demonstrated the CTLA-4 blockade allows activation of effector CD8+ T cells resulting in therapeutic anti-tumor responses [4]. A recent prospective, randomized Phase III clinical trial of an anti-CTLA-4 monoclonal antibody, Ipilimumab (Yervoy) administered alone or in combination with an HLA-A2-restricted gp100 peptide vaccine demonstrated significant improvement in overall survival compared to vaccine alone (10.1 months vs. 6.4 months, hazard ratio for death 0.66, P=0.003; 10.0 vs. 6.4 months, hazard ratio for death 0.68, P<0.001, respectively) [5]. Based on these data, Yervoy was approved for the treatment of unresectable stage III and stage IV metastatic melanoma by the FDA in 2011.

Melanoma is the 5th most prevalent cancer in the United States and accounts for approximately 5 percent of all skin cancers. However, melanoma is responsible for 80 percent of all skin cancer related deaths. The incidence of melanoma is rising rapidly and it is estimated that 68,130 people were diagnosed with and about 8,700 people died of melanoma in 2010. The median overall survival for patients with metastatic disease is approximately 6-12 months. There are three FDA approved agents for the treatment of metastatic melanoma. Dacarbazine (DTIC) is an alkylating agent that was approved in 1974. DTIC results in objective responses in 5-20% of patients but the median duration of response is generally 6 months [6]. In 1998 high-dose bolus IL-2 was approved for melanoma and induces objective responses in 15-20% of patients but these are

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associated with durable complete responses in 7-10% of patients. In 2011 the anti-CTLA-4 monoclonal antibody Ipilimumab was approved based on randomized Phase III data demonstrating a survival benefit when compared to peptide vaccine therapy. A large number of randomized clinical trials have been performed combining IL-2 with cytotoxic chemotherapy regimens but so-called biochemotherapy has not demonstrated a survival in any prospective randomized clinical trial [7-12].

1.2 Product Development Rationale

The rationale for IL-2

In the late 1970's it was shown that human peripheral blood lymphocytes exposed to IL-2 resulted in the generation of lymphocytes (lymphokine-activated killer, LAK, cells) capable of lysing fresh autologous tumors *in vitro* [13]. This observation was followed by *in vitro* data demonstrating regression of pulmonary metastases from transplanted murine sarcoma and B16 melanoma tumor cells in mice injected with IL-2-stimulated lymphocytes [14]. Subsequent studies showed the ability of directly administered, high-dose IL-2 to generate LAK cells in mice, and to mediate regression of established metastatic deposits, although a strong dose-response relationship was not observed [15].

After performing phase I studies confirming the safety of IL-2 and the adoptive transfer of LAK cells, a pilot study of the combination in the treatment of advanced cancer was published in 1985 [16]. Rosenberg et al. treated 25 patients with a variety of refractory tumors, including 7 with melanoma. Partial responses were seen in 11 of the 25 patients (7 of 11 had melanoma), and complete tumor regression was seen in one patient with metastatic melanoma. Encouragingly, the responses seemed to be durable. Lotze et al. described the treatment of ten patients with metastatic cancer with high-dose bolus IL-2 alone [17]. Three of the six patients with melanoma had objective disease regression, while no responses were seen in those patients with colorectal or ovarian cancer. Biopsy of regressing lesions revealed a marked lymphocytic infiltrate. Subsequently, the same group published data collected in the treatment of 157 patients with either single-agent high-dose IL-2 or IL-2 plus autologous transfer of LAK cells [18]. Of the 106 patients treated with combination therapy, 21.6% had an objective response including 7.5% who had complete responses. Meanwhile, 46 patients were treated with IL-2

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alone; one patient (2.1%) had a CR, and 10.8% had partial responses, for an overall response rate of 13%. In both cohorts, complete responses were of prolonged duration.

On this basis, a series of clinical trials investigating the efficacy of single-agent high-dose IL-2 were performed between 1985 and 1993, at 22 institutions including the Surgical Branch of the National Cancer Institute and elsewhere. Rosenberg et al. evaluated 409 consecutive patients with melanoma or renal cell cancer treated with intravenous bolus IL-2 (720,000 IU/kg every eight hours, up to 14 doses over 5 days) at the National Cancer Institute from 1985 to 1996 [19]. In an updated analysis of this cohort through the fall of 1996, with follow-up ranging from 3 to 11 years, the overall response rate was 16%, including 17 complete responses (6%) [19]. Of the 11.7% of melanoma patients who had a complete response, 83.3% remained in an ongoing continuous remission at the time of publication, from 70 to 148 months. In the extramural clinical trials, a total of 270 patients with metastatic melanoma were treated with IL-2 at doses ranging from 360,000 to 720,000 IU/kg, intravenously over 15 minutes every 8 hours for up to 14 consecutive doses over five days as tolerated, with maximal supportive care including pressors [20]. A second treatment cycle was administered after 6 to 9 days of rest, with further course given every 6 to 12 weeks in stable or responding patients. Median duration of response was not reached at time of analysis for those achieving a complete response, and was nearly 6 months for those with partially-regressed disease. Responses were seen in all sites of disease and in patients with heavy tumor burden. Median survival for the total group was 11.4 months, and with a median follow-up of more than 5 years, nearly half the responding patients were still alive, with 15 having survived more than 5 years. On the basis of these studies, and particularly the extended duration of observed complete responses, the Food and Drug administration approved the use of high-dose bolus IL-2 for the treatment of metastatic melanoma in 1998. Further follow-up on these pivotal studies suggested that patients can achieve durable long-term benefit from IL-2. After a median follow-up time for surviving patients that exceeded 7 years, the median duration of response for 43 responding patients and the 26 patients with partial responses in the pivotal IL-2 trials remained unchanged at 8.9 and 5.9 months, respectively [21]. Response durations ranged from 1.5 to > 122 months and disease progression had not been observed in any patient who was responding as of the last report or in any patient responding for longer than 30 months. [21].

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In these early trials, the most severe toxicities were related to a vascular leak syndrome that resembled the manifestations of septic shock. Sixty-four percent of patients experienced hypotension, while 1% suffered grade 4 hypotension. Other severe toxicities included mental status changes, tachyarrythmias, and respiratory events, but these were rare, occurring in less than 4% of patients. Nausea, vomiting, and diarrhea were common, but were not life-threatening. Elevations of serum creatinine and bilirubin were frequent but did not lead to chronic organ dysfunction. Infections were seen in 15% of all patients, with bacterial sepsis due to Staphylococcus aureus leading to 6 treatment-related deaths. In 1990, antibiotic prophylaxis became standard practice during IL-2 therapy and treatment-related mortality decreased significantly [22]. There are now well established treatment guidelines for the prevention and management of IL-2-related toxicity [23]. Of note, the investigators on this protocol are all highly experienced IL-2 clinicians.

Rationale for targeting CTLA-4 in Melanoma

The activation of T cells is a complex and highly regulated process that begins when a T cell receptor recognizes its cognate antigen in the form of a processed peptide bound to a major histocompatibility complex (MHC) on the surface of a professional antigen-presenting cell (APC). This interaction has been termed "Signal 1" and complete T cell activation occurs only when a second co-stimulatory signal or "Signal 2" occurs. This is best characterized by the B7.1 and B7.2 co-stimulatory molecules on APCs that bind to CD28 on the surface of a T cell. CD28 induces cell cycle progression, T cell proliferation and production of IL-2. Following activation, the cytotoxic T lymphocyte antigen 4 (CTLA-4) is mobilized to the cell surface and inhibits T cell activation (see Figure 1). CTLA-4 mediates T-cell inhibition through competition with CD28 for B7 and through specific inhibitory signaling [24-31]. In addition to inhibiting effector T-cell activation and proliferation, CTLA-4 engagement also results in down-regulation of IL-2 gene transcription. This immunologic "checkpoint" limits T cell activation to areas where there is inflammation or injury mediating peripheral tolerance that protects normal tissue and tumor cells against adaptive immune responses [32]. The potential antitumor effects of CTLA-4 blockade were confirmed in preclinical tumor models where administration of CTLA-4–blocking antibodies resulted in the regression of several highly immunogenic tumor types in mice [33-34].

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However, CTLA-4 antibody blockade alone has had minimal effects in the poorly immunogenic B16 melanoma unless CTLA-4 blockade is combined with vaccination with GM-CSF [35-37]. This suggests that in some tumors that have been heavily immunoedited, or are poorly immunogenic, CTLA-4 blockade may need to be combined with other strategies. The immunological studies suggested the CTLA-4 blockade alone may potentiate both Tregs and effector T-cells, whereas CTLA-4 blockade coupled with GM-CSF shifted the ratio of tumor specific T effector to Tregs [38-39]. These encouraging data led clinical anti-CTLA-4 antibody trials in cancer patients. Ipilimumab, a fully humanized (human) monoclonal antibody, demonstrated antitumor activity in patients with advanced melanoma response rates range from about 5% to 29% by standard RECIST or WHO response criteria as monotherapy or in combination with chemotherapy [40-43]. Recent clinical data suggest that patients with advanced melanoma benefited from 4 dosage of ipilimumab at 10 mg/kg injected every 3 week with prolonged median overall survival from 8.9 to possibly longer than 15.5 months [44-46]. Furthermore, with ipilimumab treated patients with stable disease and those with slow regression that did not meet strict RECIST or WHO criteria for response have had prolonged time to progression. In a prospective, randomized Phase III clinical trial of an anti-CTLA-4 monoclonal antibody, Ipilimumab (Yervoy) administered alone or in combination with an HLA-A2-restricted gp100 peptide vaccine demonstrated significant improvement in overall survival compared to vaccine alone (10.1 months vs. 6.4 months, hazard ratio for death 0.66, P=0.003; 10.0 vs. 6.4 months, hazard ratio for death 0.68, P<0.001, respectively) [5]. Based on these data, Yervoy was approved for the treatment of unresectable stage III and stage IV metastatic melanoma by the FDA in 2011.

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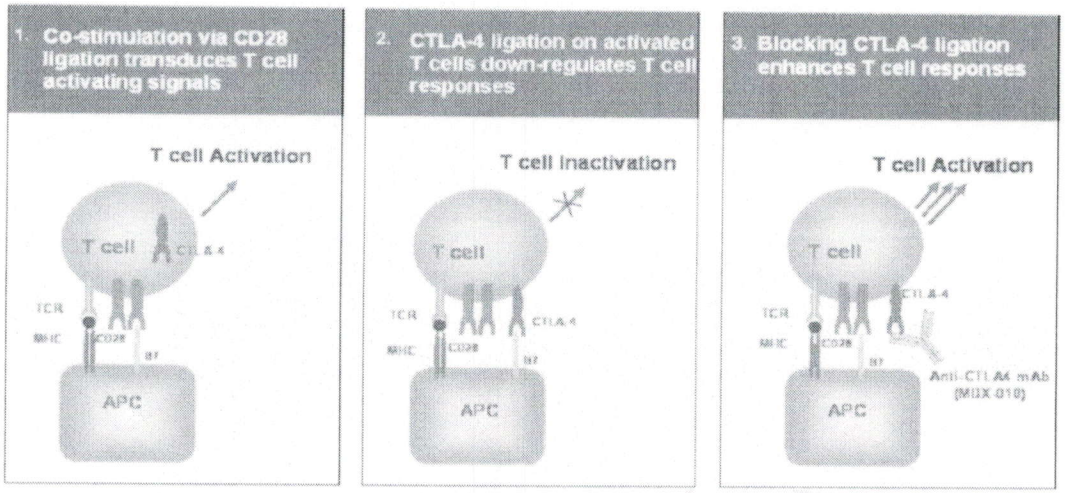
1.2.1 CTLA-4 and T Cell Activation

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) [47]. (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 failsafe mechanism for maintenance of peripheral T cell tolerance, insuring that T cell activation can only be stimulated by appropriate APCs [48]. The fact that tumor cells do not express B7 contributes to their poor capacity to elicit immune responses [49-50].

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) B7expressing 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

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cells by radiation has been shown to destroy the immuno-enhancing activity of the B7 gene product [51-52].

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 [53]. 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 [54]. 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 [55-58]. Blocking CTLA-4-B7 interaction while preserving signaling via CD28 resulted in enhanced T cell responses *in vitro* [56].

Perhaps the most convincing demonstration of the down-regulatory role of CTLA-4 came from examination of mice with a null mutation [59-61]. 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 CTLA4deficient mice, the rampant T cell expansion that occurs in the mice indicates that CTLA4 plays a critical role in down-regulating T cell responses in the periphery [58].

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.

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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 MDX010015 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.

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1.3.4 Clinical Safety with Ipilimumab

Ipilimumab immunotherapy is currently under investigation in patients with unresectable advanced melanoma (unresectable Stage III or Stage IV) to potentially demonstrate an improvement on a large unmet medical need in this population.

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

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

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

Table 1: Ipilimumab - Overall Summary of Safety

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

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1.3.4.a Details of Drug-Related Adverse Events

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

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

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

1.3.4.b Details of Drug-Related Serious Adverse Events

Among all 2901 treated subjects, SAEs considered possibly, probably, or definitely related to study drug were reported for 20.5% of subjects. Drug-related SAEs reported in at least 1% of the 2901 subjects included diarrhea (5.8%), colitis (4.7%), ALT increased (2.3%), AST increased (2.2%), pyrexia (1.6%), and vomiting (1.3%). Among the 658 subjects who received ipilimumab at 10 mg/kg, SAEs considered possibly, probably, or definitely related to study drug were reported for 27.2% of subjects. Drug-related SAEs reported in at least 1% of the 658 subjects treated at 10 mg/kg included diarrhea (8.5%), colitis (7.0%),vomiting (2.1%), AST increased (2.1%), ALT increased (2.0%), autoimmune hepatitis (2.0%), pyrexia (1.8%), hypopituitarism (1.7%), dehydration (1.7%), nausea (1.2%), and abdominal pain (1.1%).

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.

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

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

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

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

		Number of Subjects (%)	
		Ipilimumab 0.3 - 20 mg/kg	Ipilimumab 10 mg/kg
		N = 2901	N = 658
	irAEs[a]		
	Any	441 (15.2)	144 (21.9)
	Grade 3	298 (10.3)	87 (13.2)
	Grade 4	59 (2.0)	25 (3.8)
	GI irAE[a]		
	Any	236 (8.1)	85 (12.9)
	Grade 3	166 (5.7)	58 (8.8)
	Grade 4	17 (0.6)	10 (1.5)
	Liver irAE[a]		
	Any	109 (3.8)	33 (5.0)
	Grade 3	72 (2.5)	18 (2.7)
	Grade 4	32 (1.1)	13 (2.0)
	Endocrine irAE[a]		
	Any	61 (2.1)	21 (3.2)
	Grade 3	44 (1.5)	12 (1.8)
	Grade 4	3 (0.1)	1 (0.2)

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

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

Corticosteroid treatment did not adversely affect antitumor responses in those subjects who had both an irAE requiring steroid therapy and an objective tumor response. Systemic corticosteroids do not appear adversely associated with ipilimumab-induced clinical response when used to manage irAEs in patients with advanced melanoma.

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Similar results were observed regardless of whether mWHO or the immune-related response criteria (irRC) were used. Steroids can be used promptly to manage severe irAEs and minimize the risk for serious complications [62].

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

Gastrointestinal irAEs

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

Inflammatory Hepatotoxicity

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

Hypophysitis/Hypopituitarism and Other Endocrine Conditions

Hypophysitis/hypopituitarism, clinically manifested by fatigue, has been reported. Most subjects with hypopituitarism presented with nonspecific complaints such as fatigue, confusion, visual disturbance, or impotence. Some had headache as the predominant presentation. The majority of subjects with hypopituitarism demonstrated enlarged pituitary glands based on brain magnetic resonance imaging (MRI). Low adrenocorticotropic hormone (ACTH) and cortisol were the most common biochemical abnormality reported; low thyroid stimulating hormone (TSH), testosterone, or prolactin was also reported in some subjects [63].

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

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

Rash and Other Skin Conditions

Rash was one of the most common irAEs, and most cases were Grade 1 or 2 in intensity; pruritus has also been reported [64]. When biopsied, pleomorphic infiltrates were noted in the skin. Among subject who received ipilimumab at 10 mg/kg, skin irAEs of any grade were reported for 52.9% (348/658) of subjects, and Grade 3 - 4 skin irAEs were reported for 2.9% (19/658) of subjects. Serious skin irAEs were reported in < 1% (4/658) of subjects who received ipilimumab at 10 mg/kg. Skin irAEs were generally reversible.

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

Other reported irAEs

Ocular inflammation, manifested as Grade 2 or Grade 3 episcleritis or uveitis, was associated with concomitant diarrhea in a few subjects and occasionally occurred in the absence of clinically apparent GI symptoms [65]. Serious ocular inflammation was reported in 1 of 658 (0.2%) subjects who received ipilimumab at 10 mg/kg (8 [0.3%] of 2901 subjects program-wide reported serious occular inflammation). Preliminary analysis (based on the manual extraction of the SAE data from the internal safety database) indicated that the median time to event onset was approximately 61 days (range: 14 - 114 days). Based on the available data with known outcome, most of the subjects recovered or improved with or without corticosteroid therapy with a median duration of approximately 6 days (range: 5 - 23 days).

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

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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.a Drug-Related Deaths

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

1.3.5.b 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 CA184022 in which three dose levels of ipilimumab were studied, including 0.3 vs 3 vs 10 mg/kg. Table 3 summarizes the overall irAE frequencies by dose from CA184022 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 3 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.

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Table 3. Summary of Immune-Related Adverse Events (irAEs) by Treatment Groups - Treated Subjects (CA184022)			
	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.c Neuropathies

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

1.3.6 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 and the principal demonstration of the efficacy of ipilimumab at the 10 mg/kg dose comes from 3 Phase 2 multicenter trials in 487 subjects with advanced melanoma: CA184022 [66], CA184008 [67] and CA184007 [68].

CA184022 was a dose-ranging trial in which subjects were randomized (1:1:1) to a high (10 mg/kg) intermediate (3.0 mg/kg), and low (0.3 mg/kg) ipilimumab dose. CA184022 and CA184008 enrolled pretreated subjects and efficacy data at 10 mg/kg are pooled for these studies; CA184007 enrolled a mixed population of pretreated and previously

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untreated subjects. In all 3 studies, ipilimumab as monotherapy was administered by intravenous (IV) infusion every 3 weeks for 4 doses (induction), followed by a dose every 12 weeks (maintenance).

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

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

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

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

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

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

Consistent with the known mechanism of action of ipilimumab, the reduction in tumor burden in the 3 primary melanoma studies was characterized by novel patterns of measurable clinical effect. In addition to objective response (complete response [CR] and partial response [PR]), and SD as measured by mWHO, novel patterns of clinical activity, which are related to the immunological mechanism of action of ipilimumab, were reported in all 3 studies. These patterns of activity were characterized by overall reductions from baseline in total tumor burden (index plus measurable new lesions, when present) after the appearance of new lesions and/or after an initial tumor burden increase. In the phase III clinical trial ipilimumab at a dose of 3 mg/kg was associated with an overall objective response rate of 10.9% [5]. Of 227 treated subjects who received 10 mg/kg ipilimumab in studies CA184022 and CA184008, 9.7% of subjects

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demonstrated disease control after an initial increase in tumor burden and/or appearance of new lesions [66-68].

Survival data from these 3 primary studies (CA184022, CA184008, and CA184007) are supported by OS data from CA184004 and MDX010-28. Both studies enrolled previously untreated and pretreated subjects with advanced melanoma. In CA184004, 42 subjects were randomized to 10 mg/kg ipilimumab. The median follow-up for survival in this study was 8.6 months. The median OS was 11.8 months (95% CI: 6.1, --); the 1-year survival rate was 44.2% (95% CI: 24.1%, 64.1%) [69]. Data are available for 23 response evaluable subjects treated at 10 mg/kg ipilimumab in MDX010-15 who enrolled in the follow-up study MDX010-28. The median follow-up for survival in this study was 13.4 months. The median OS was 13.2 months (95% CI: 9.4, 19.4). The overall survival for 2 subjects with ongoing responses was 26.0+ months and 25.0+ months [70].

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

1.3.6.a Relationship Between Response and Immune Related Events in Patients with Metastatic Melanoma

Drug-related AEs of any grade considered to be immune-mediated in nature (irAEs) were reported for 59.6% (1729/2901) 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 best overall response (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 administered at 10 mg/kg (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 [66-68]. Generally, disease control and long term survival are observed among patients regardless of whether they do or do not develop Grade ≥ 2 irAEs.

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1.4 Safety of Interleukin-2

Interleukin-2 (Proleukin; Aldesleukin) was approved for the treatment of metastatic renal cell carcinoma in 1992 and for metastatic melanoma in 1998. There is now considerable safety information available on IL-2 and clinical algorhythms have been established to prevent and treat potential IL-2-related toxicity [72-73]. All patients contemplating treatment with IL-2 are screened for general clinical performance status, presence of active infections, presence of CNS metastases, cardiac stress testing in all patients over 50 years of age or in any patient with a clinical history or signs of underlying ischemic heart disease and pulmonary function studies in patients with a history of pulmonary disease, chronic smoking or extensive pulmonary metastases. These pre-treatment studies help to identify patients who may experience high grade toxicity during IL-2 and may exclude patients from treatment. The presence of active CNS metastases, reversible ischemic heart disease, pleural effusions, ascites and active infection are contraindications to IL-2 and such patients would not be eligible for participation in this trial.

The major adverse events related to high-dose IL-2 treatment are due to capillary leak syndrome. This is a constellation of physiologic changes characterized by hypotension, increased cardiac output, peripheral edema and multi-organ system dysfunction. The toxicity is generally self-limited and effective management strategies are available. Most patients will experience fever and chills with IL-2 administration but this side effect can be prevented or blunted by prophylactic use of acetaminophen and indomethacin, which are frequently given prior to IL-2 dosing. Hypotension can be treated with fluid challenge and intravenous pressors in refractory situations. Cardiac dysrhythmias, such as atrial fibrillation, can occur and a cardiomyositis related to IL-2 has also been reported. Patients are typically treated on telemetry to monitor their cardiac rhythm and dysrhythmias are treated through standard measures while cardiomyositis responds to non-steroidal anti-inflammatory agents. Peripheral edema is usually limited and typically responds to diuretics.

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The GI side effects include nausea, vomiting, diarrhea, hepatic dysfunction, hyperbilirubinemia, hypoalbuminemia and anorexia. Most patients are given anti-emetics prophylactically and monitored closely during therapy for signs and symptoms of GI abnormalities. These symptoms typically resolve with treatment cessation and patients can be supported by additional anti-emetics and anti-diarrheal agents if necessary. Renal side effects include oliguria, electrolyte abnormalities and elevated serum creatinine, which is usually monitored daily. Treatment usually involves fluid and electrolyte replacement and doses may be held for an elevated creatinine. These abnormalities usually resolve when treatment is stopped and active dieresis may be helpful in some cases. Additional side effects include neutropenia, thrombocytopenia, pruritis, confusion, autoimmune thyroiditis and vitiligo. Laboratory values are monitored daily and patients are closely observed clinically during active treatment. All symptoms, except for autoimmune thyroiditis and vitiligo, are temporary and resolve at the end of treatment.

Of particular concern is the development of diarrhea since ipilimumab may also result in autoimmune colitis and significant diarrhea. The mechanism of the diarrhea and kinetics of response for the two drugs, however, is different. While IL-2-related diarrhea is secretory in nature and occurs and resolves rapidly, ipilimumab-related diarrhea is inflammatory in nature and develops more slowly. There is some evidence that patients who receive ipilimumab following therapy with IL-2 do not have an increase in side effects, including diarrhea (Kaufman et al. ASCO abstract 2013). A previous clinical trial of IL-2 and ipilimumab also did not show any unexpected change in the frequency or severity of diarrhea [43].

1.5 Overall Risk/Benefit Assessment

Results from 3 primary efficacy studies of ipilimumab in advanced melanoma suggest that the 10 mg/kg dose is active and offers the best benefit to risk ratio based on a rate of disease control ranging from 27.1% to 35.1% and 2-year survival rates ranging from 29.81% to 41.78% in the context of the historical data which demonstrate a 2year survival rate of approximately 8% to 18% in subjects with previously untreated advanced melanoma [74-77]. 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

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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.

1.6 Study Rationale

The goal of this study is to determine if there is a clinical benefit to combining high-dose IL-2 with ipilimumab in patients with metastatic melanoma. A previous Phase I/II clinical trial was conducted to evaluate this combination in patients with metastatic melanoma [43]. In this trial, 36 patients received ipilimumab every three weeks for a total of three doses in a dose escalation manner with three patients receiving 0.1, 0.3, 1.0 or 2.0 mg/kg. An additional 24 patients received ipilimumab at 3 mg/kg, the MTD tested and achieved in this trial. All patients received high-dose bolus IL-2 at 720,000 IU/kg every 8

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hours to a maximum of 15 doses. The IL-2 was administered immediately following the second and third infusions of Ipilimumab. This trial did not allow maintenance Ipilimumab treatment. Of the 36 patients treated, 8 (22%) demonstrated objective tumor regression with 3 complete and 5 partial objective responses. These responses included patients with soft tissue and visceral disease. Six of the 8 patients were reported to have ongoing objective responses at 11-19 months following the trial. There were five patients (14%) who developed grade III or IV autoimmune events following treatment and there were no treatment-related deaths.

The NCI suggests that the combination is feasible and may be associated with meaningful therapeutic responses with a comparable rate of autoimmune toxicity. This study, however, may underestimate the potential of this combination for several reasons. The maximum Ipilimumab dose used was 3 mg/kg and there is now evidence that 10 mg/kg may be associated with a higher clinical response rate. Current data from Ipilimumab clinical trials also suggests that a minimum of four cycles of treatment are needed for induction and many patients benefit from maintenance Ipilimumab administration. Further, it is possible that responses may be delayed following Ipilimumab treatment and, thus later follow-up is required to fully determine the therapeutic impact of treatment. Thus, this clinical trial will be designed to better define the optimal dose and schedule of Ipilimumab with appropriate clinical follow-up to better determine the potential for combination treatment in melanoma.

The overall risk-benefit ratio for patients entering this protocol is therefore at least comparable to and possibly better than alternative options. In the current clinical trial, we plan to confirm that **the combination of high-dose IL-2 and Ipilimumab will result in improved clinical outcomes for patients with metastatic melanoma** using a larger cohort of subjects and a higher dose of ipilimumab. We will also test the hypothesis that combination Proleukin/Yervoy is feasible and safe in patients with advanced melanoma, induces tumor-specific immunity, and leads to long-term T cell memory and inhibition of $CD4^+CD25^+$ regulatory T cells.

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2. STUDY OBJECTIVES

2.1 Primary Objective

The primary clinical endpoint will be the best overall response rate within the first 24 weeks of combination IL-2 and ipilimumab using the immune-related response criteria. The rationale for this endpoint is based on recent data suggesting a delayed kinetic pattern of tumor regression with immunotherapy agents, such as ipilimumab. The combination is expected to result in more objective responses.

Preliminary safety assessment will be performed on the first 6 patients before other patients are allowed o to enter the study

2.2 Secondary Objectives

The following secondary objectives will also be determined in this trial:

Clinical Response

In addition to the primary objective, secondary clinical endpoints of efficacy will be collected in an exploratory manner as follows:

Best overall response (BOR): Since responses may exhibit delayed kinetics it is possible that standard response reporting may miss a non-traditional tumor regression with the planned reporting criteria. We will, therefore, collect the best overall response for each subject at any point during their study involvement in case patients develop a delayed response after the first 24 weeks.

Progression-free survival (PFS): Progression-free survival will be assessed using Kaplan Meier plots and based on mWHO criteria for disease progression. The progression-free survival rates will be presented, together with the 90% confidence intervals. If appropriate, medians and 90% confidence interval will also be presented.

Disease control rate (DCR): Since it is known that PFS may be an inappropriate endpoint for ipilimumab and other forms of immunotherapy, we will also collect data on disease control rate defined as the rate of complete, partial and stable disease responses.

Overall survival: Overall survival will be assessed using Kaplan Meier plots at 1, 2 and 3 years.

Safety and Feasibility

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A secondary objective will be to collect data on the safety and feasibility of combined high-dose IL-2 and ipilimumab. The type of toxicity, frequency and severity will be noted in the intention-to-treat population. Toxicities will include abnormal hematology and biochemistry laboratories, which will be recorded at baseline and at various visits throughout the study. Adverse events will be listed by subjects within groups showing time of onset, period of event, grade classified using the CTCAE v.4.0, relationship to disease and outcome. The number of events in each classification of severity and relationship to treatment will be tabulated for each patient.

Preliminary safety assessment will be performed on the first 6 patients before other patients are allowed o to enter the study

Immune Responses

To evaluate the CD4+ and CD8+ T cell response in the tumor microenvironment and peripheral blood of patients treated on this study. Evaluation of immune responses will be primarily based on the breadth and magnitude of T cell responses compared from post-treatment with both agents to baseline levels. The frequency of activated effector CD8+ T cells and CD4+ regulatory T cells will be measured pre-treatment and at selected time points post-treatment in the peripheral blood, and in the tumor microenvironment in selected patients who agree to and have easily accessible tumors for serial biopsy. MART-1-specific CD8+ T cells will also be determined by tetramer or dextramer analysis and selected patients (HLA-A2+) will have antigen-specific responses determined by MART-1, gp100 and/or tyrosinase tetramer analysis and intracellular cytokine staining. In non-A2+ subjects we will use overlapping peptides in an interferon-gamma ELISPOT assay, or alternatively will perform intracellular interferon-γ staining. Treatment effect for each patient will be measured as paired differences between pre- and post-measurements at each site. Transformation of the data will be performed if appropriate, e.g. log transformation, and hence treatment effect will be expressed on a log scale.

3. STUDY DESIGN

The study will be an open label, single arm trial in which patients will be treated as

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follows:

InductionTreatment: Ipilimumab (10 mg/kg) for 4 cycles (Days 1, 22, 43, 64) and high-dose IL-2 (600,000 IU/kg) for 2 cycles (Days 22-26, 43-47).

On days when both drugs are scheduled, the ipilimumab should be administered first followed by IL-2 at least 4-6 hours later.

Beginning on week 24, patients without disease progression or unacceptable toxicity will receive maintenance ipilimumab (10 mg/kg) IV over 90 minutes. Treatment repeats every 12 weeks in the absence of disease progression or unacceptable toxicity after the treatment induction period and this does not pertain to after maintenance ipilimumab treatment.

The trial will be conducted in three phases, as described below:

- **Screening**

  During the screening phase, each patient will be assessed for eligibility to participate as determined by the inclusion/exclusion criteria (Section 4). Patients will also undergo baseline imaging, blood work, urinalysis, EKG and peripheral blood/tumor (when feasible) collection for immune monitoring analysis. The informed consent must be reviewed with the subject, signed, dated and the patient given a copy of the signed consent form. Once the consent is signed, a copy will be submitted to the Theradex® IWRS sytem and a patient number assigned. This number will be used on all case report forms for the subject.

  All patients must be registered in the Theradex® Interactive Web Response System (IWRS). Patient enrollment information must be entered in the Theradex® Interactive Web Response System (IWRS) prior to first study drug administration. This information will serve to confirm patient eligibility and initiate the enrollment process. Once the Theradex® IWRS system verifies eligibility, a unique patient study number will be issued. The patient will not be identified by name. This is the point that the patient is considered on study The patient will be considered on study as of IP start..

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Patients must not start protocol treatment prior to registration. See the Study Operations Manual for further information on Patient Enrollment.

Patient demographic information, the signed and dated study-specific eligibility checklist and completed signature page of the consent form and additional source documents if requested by CINJ Regulatory Coordinator must be sent to the registration desk. Site should retain source document copies of all original eligibilities, consents and registration paperwork.

Protocol Number

Investigator Identification

- Institution and affiliate name
- Investigator's name

Patient Identification

- Patient's initials and registration number
- Patient demographics
  - Sex
  - Birth date (mm/yyyy)
  - Race
  - Ethnicity
  - Nine-digit ZIP code
  - Method of payment

Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 4.0. An eligibility checklist has been appended to the protocol.

Additional Requirements

Patients must provide a signed and dated written informed consent form.

Pathology reports must be submitted as indicated in Section 12 for review.

Blood and tumor samples are to be submitted for banking per patient consent as indicated in Section 12

Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and

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follow-up data will not be collected. However, the reason for not starting protocol treatment must be documented on the off treatment form. Also the date and type of the first non-protocol treatment that the patient receives will be reported

- **Ipilimumab Induction**
  - The recommended induction dose of ipilimumab as a single agent is 10 mg/kg administered intravenously over a 90 minute period every 3 weeks for a total of four doses, as tolerated.
  - Laboratory evaluations should be performed and the results examined before administration of each ipilimumab dose.
  - As durable disease stabilization and/or objective tumor response can be seen after early progression before Week 12, it is recommended that, in the absence of dose limiting toxicities (e.g. serious irAEs), all four doses of ipilimumab be administered over the initial 12 weeks even in the setting of apparent clinical progression, providing the subject's performance status remains stable.
  - All subjects who enter the induction period, including those who may have discontinued treatment for drug-related AEs and/or who have evidence of clinical progression during the induction period, should obtain a 12 week tumor assessment.
  - Based on clinical experience in the ongoing and completed melanoma studies, the following recommendations apply for subject management in light of the Week 12 or later tumor assessments.

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- The appearance of new lesions in subjects with other stable or shrinking baseline tumor burden may be experiencing clinical benefit and should continue in follow-up and/or maintenance therapy before alternative anticancer agents are considered. These subjects can be seen to have continued tumor shrinkage in follow-up scans.
- As long as overall tumor burden is stable or decreasing, subjects should remain in follow-up and/or maintenance (see below), even in the presence of new lesions.
- Clinical progression warranting alternative anti-cancer treatment should be considered only in subjects whose overall tumor burden appears to be substantially increased and/or in subjects whose performance status is decreased.

- **Ipilimumab Maintenance** As per the schedule of dosing in the ongoing and completed clinical studies using ipilimumab in subjects with pretreated advanced melanoma, at Week 24, maintenance therapy should be offered to all subjects who have not experienced unacceptable toxicity (refractory Grade > 3 irAEs) and are considered by the investigator to be obtaining clinical benefit, either because of apparent tumor stability or continued shrinkage and/or late response.
- A single dose of 10 mg/kg ipilimumab given intravenously over 90 minutes should be administered every 12 weeks, starting from Week 24 until the subject is no longer clinically benefiting from therapy, per the investigator, or until the occurrence of unacceptable or unmanageable toxicity.Subjects in maintenance should receive radiographic tumor assessments every 12 weeks before administration.

- **Interleukin-2 Treatment**
  - Interleukin-2 will be administered according to standard institutional guidelines and in accord with current clinical practice guidelines for IL-2 administration.
  - IL-2 will start on the same day as cycle 2 and 3 of ipilimumab. In general patients can receive ipilimumab in the morning and be admitted in the afternoon for IL-2 therapy the same day. IL-2 will begin after pre-medication and will be given as a 15 minute bolus intravenous infusion every 8 hours until a maximum of 14 doses or unacceptable toxicity occurs according to institutional protocol for IL-2 administration.

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- IL-2 dosing is 600,000 I.U./kg and will be based on baseline weight (in kilograms) upon hospital admission for treatment. IL-2 will be held for toxicity as per institutional guidelines. The total number of IL-2 doses should be recorded for each cycle of treatment.
- Special attention should be paid to the development of diarrhea in patients treated with IL-2 since ipilimumab may also result in diarrhea. Since IL-2 diarrhea is generally secretory and ipilimumab-related diarrhea is generally inflammatory the assignment of causality may require stool analysis for white blood cells and/or endoscopy with visualization of the colon mucosa with or without a biopsy. A low threshold for diarrhea work-up and management should be used in this trial

- **Follow-up** (duration of study).
  - Subjects who are no longer receiving ipilimumab because of unacceptable toxicity (refractory Grade > 3 irAEs) or due to investigator judgment are managed in long term survival follow-up. Efficacy assessments for these subjects during follow-up are as per the standard of care. Date of death is recorded. If patient are not able to come to clinic, then long term survival follow up will be conducted by phone every 6 months.
  - Subjects who discontinue ipilimumab treatments should be followed until death or the closure of the study (whichever is first).
  - Subjects who are no longer receiving ipilimumab because of clinical progression and who have switched to alternative treatment are not followed formally except to record the date of death.

4. SUBJECT SELECTION CRITERIA

4.1 Inclusion Criteria

1) Willing and able to give written informed consent.
2) Histologic or cytologic diagnosis of cutaneous melanoma that is considered unresectable (Stage III) or metastatic (Stage IV). Ocular and mucosal melanoma is excluded.
3) Required values for initial laboratory tests:
   - WBC ≥ 2000/uL
   - ANC ≥ 1000/uL

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- Platelets ≥ 75 x 10^3/uL
- Hemoglobin ≥ 9 g/dL (≥ 80 g/L; may be transfused)
- Creatinine ≤ 2.0 x ULN
- AST/ALT ≤ 2.5 x ULN for patients without liver metastasis,
- ≤ 5 times for patients with liver metastases
- Total Bilirubin ≤ 2.0 x ULN, (except patients with Gilbert's Syndrome, who must have a total bilirubin less than 3.0 mg/dL)

4) No known active or chronic infection with HIV, Hepatitis B, or Hepatitis C. Testing is not required unless clinically suspected.
5) Performance status (ECOG 0-1; see Appendix for table).
6) Patients must have a life expectancy of greater than three months at the start of the trial.
7) Patients must have a brain MRI or CT (with and without contrast) that is free of active metastases. Metastases that have been treated with radiation or surgical resection, are stable for at least 4 weeks and do not require steroids are eligible.
8) Patients may have received treatment of completely resected early stage melanoma, comprising interferon, radiation treatment, or experimental vaccine therapy, and in the metastatic setting patient can have had treatment such as chemotherapy, immunotherapy (except prior treatment with Ipilimumab and IL-2), and other experimental agent which was completed 4 weeks prior to enrollment.
9) Normal cardiac stress test for patients over 50 years of age.
10) Pulmonary Function: FEV1 and FVC > 65% of prediction for those patients with extensive pulmonary metastases or chronic pulmonary disease history.
11) Men and women, ≥ 18 years of age.

    Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the study and for up to 26 weeks after the last dose of investigational product, in such a manner that the risk of pregnancy is minimized. *In general, the decision for appropriate methods to prevent pregnancy should be determined by discussions between the investigator and the study subject.*

    WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation,

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[redacted]) or is not post-menopausal. Post-menopause is defined as:

- Amenorrhea ≥ 12 consecutive months without another cause, or
- For women with irregular menstrual periods and taking hormone replacement therapy (HRT), a documented serum follicle stimulating hormone (FSH) level ≥ 35 mIU/mL.

Women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or are practicing abstinence or where their partner is sterile (eg, vasectomy) should be considered to be of childbearing potential.

WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours before the start of ipilimumab.

Men of fathering potential must be using an adequate method of contraception to avoid conception throughout the study [and for up to 26 weeks after the last dose of investigational product] in such a manner that the risk of pregnancy is minimized.

4.2 Exclusion Criteria

1) Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit study compliance
2) Any other malignancy form which the patient has been disease-free for less than 5 years, with the exception of adequately treated and cured basal or squamous cell skin cancer, superficial bladder cancer or carcinoma in situ of the cervix.
3) Patients with primary ocular or mucosal melanoma are excluded.
4) Autoimmune disease: Patients with a history of inflammatory bowel disease, including ulcerative colitis and Crohn's Diseasse, 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. Guillain-Barre Syndrome and Myasthenia Gravis).

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5) 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.

6) Patients with underlying heart conditions who are deemed ineligible for surgery by cardiology consult. Patients with reversible ischemic changes on cardiac stress test.

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

8) A history of prior treatment with IL-2, ipilimumab or prior CTLA4 inhibitor or agonist for metastatic disease. Prior therapy with ipilimumab in the adjuvant setting is allowed provided there were no Grade 3 or greater adverse events that did not resolve with limited corticosteroid use; and more than 6 months have elapsed since final adjuvant treatment and start of study treatment on this protocol.

9) Concomitant therapy with any of the following: interferon, or other non-study immunotherapy regimens; cytotoxic chemotherapy; immunosuppressive agents; other investigation therapies; or chronic use of systemic corticosteroids. Immunosuppressive agents should be stopped within 4 weeks of randomization. Steroids should be stopped 14 days prior to beginning ipilimumab therapy.

10) Women of childbearing potential (WOCBP), defined above in Section 4.1, who:

    a. are unwilling or unable to use an acceptable method of contraception to avoid pregnancy for their entire study period and for at least 8 weeks after cessation of study drug, or

    b. have a positive pregnancy test at baseline, or

    c. are pregnant or breastfeeding.

11) Prisoners or subjects who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (eg, infectious) illness.

4.3 Data Safety Monitoring Plan

The Rutgers Cancer Institute of New Jersey has established a Data and Safety Monitoring Plan (DSMP) for the conduct of clinical trials in patients with cancer. A dedicated Data Safety Monitoring Committee (DSMC) will serve as the data safety monitoring board for this clinical trial. All unexpected and serious adverse events will be

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reported to the DSMC (as well as each institutional IRB and study sponsor) according to the reporting requirements detailed in Section 8.0 of this protocol and per the [redacted] DSMP. An independent DSMB will also be established composed of all study site principal investigators, two independent physicians familiar with tumor immunotherapy clinical trials and one biostatistician for external review of the safety data. An interim safety analysis will be conducted after the first 6 patients are enrolled. The independent DSMB will review the safety data and if concerns are found, the independent DSMB may recommend that the ipilimumab dose be reduced to 3 mg/kg.

5. DRUG ADMINISTRATION GUIDELINES

5.1 Ipilimumab

Each patient will receive ipilimumab at 10 mg/kg by intravenous infusion. Infusions should be given over 90 minutes (not bolus or IV push).

Dose Calculations

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. All calculations should be based on screening weight. As long as any weight changes are 10% or less from screening weight, further dosing can be based on the screening weight.

5.1.1 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. In preparation of infusion, ipilimumab may be stored in IV infusion bags (PVC, non-PVC/non-DEHP) or glass infusion containers at room temperature or refrigerated (2°C - 8°C) for up to 24 hours. Drug must

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be completely delivered to the subject within 24 hours of preparation. This includes any time in transit plus the total time for the infusion.

As with all injectable drugs, care should be taken when handling and preparing ipilimumab. Whenever possible, it 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 of at the site following procedures for the disposal of anticancer drugs.

5.1.2 Preparation and Administration Guidelines

The supplies needed for ipilimumab preparation and administration include calibrated syringes and infusion containers. Ipilimumab is to be administered as an IV infusion using a volumetric pump through a 0.2 or 1.2 micrometer in-line filter (supplied by site) at the 10 mg/kg dose (or placebo equivalent). See the current Investigator Brochure for additional information on allowable filter types. The infusion must be completed in 90 minutes with a 10 ml normal saline flush at the end. The ratio and rate will be specified in the pharmacy manual. The total dose must be calculated using the most recent subject weight (obtained within 3 days of the dosing visit, and prior to the infusion).

As ipilimumab is stored at refrigerated temperatures (2-8°C), allow the appropriate number of vials of ipilimumab to stand at room temperature for approximately five minutes.

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].

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.

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

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patient. For example, if preparing a 10mg/kg treatment for a 65 kg patient you will use over 3 vials (or 650 mg), the drug solution volume will be 10 mL per vial or 130 mL total.

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.

Mix by GENTLY inverting several times. DO NOT shake.

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.

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

Dose de-escalation of IL-2 from 600,000 IU/kg or ipilimumab from 10 mg/kg is not allowed.

5.1.3.a Ipilimumab Dose Delay Rule

Decisions to skip an ipilimumab dose must be made on specified safety criteria. Treatment with ipilimumab will be skipped or discontinued if the subject experiences at least one adverse event, specified below, considered by the investigator to be **"possibly", probably" or "certainly" related to ipilimumab treatment.** The investigator should contact the study PI and/or BMS for any adverse event that will prompt a skipped dose or discontinuation of ipilimumab.

The following criteria will be used to determine dose skipping, restarting doses, or discontinuing ipilimumab. Patients who require steroids must be discussed with the medical monitor of the trial prior to re-treating with ipilimumab.

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 irAEs), except for laboratory abnormalities Any ≥ Grade 3 laboratory abnormality

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- Any adverse event, laboratory abnormality or intercurrent illness that, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued dosing.

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

- Any ≥ Grade 3 skin related adverse event regardless of causality, unless reversible within 3 weeks.

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

- If the *adverse event has resolved*, restart ipilimumab dosing at the next scheduled timepoint 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 skipped and dosing will be resumed at the subsequently scheduled dose.
- If > 1 dose is expected to be skipped, the dosing schedule modifications must be discussed with the principal investigator prior to implementation.

5.1.4 Discontinuation of Study Therapy

It is possible that either IL-2 or ipilimumab may need to be discontinued for specific drug-related toxicity in a given cycle. Any decision to discontinue a drug should be made in consultation with the medical monitor for the study. General guidelines are provided below.

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)
- The occurrence of any grade 4 adverse event related to IL-2 that does not decrease to grade 1 within 4 weeks of completing IL-2 therapy
- 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

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- Pregnancy
  - All WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation. Institutional policy and local regulations should determine the frequency of on study pregnancy tests for WOCBP enrolled in the study.
  - The investigator must immediately notify BMS in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by [redacted]
- Imprisonment or the compulsory detention for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

5.1.5 Permanent Discontinuation of Ipilimumab

5.1.5.a Permanent Discontinuation for Related Adverse Events

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

- Any ≥ Grade 2 eye pain or reduction of visual acuity that does not respond to topical therapy and does not improve to ≤ Grade 1 severity within 2 weeks of starting therapy, OR, requires systemic treatment.
- Any ≥ Grade 3 bronchospasm or other hypersensitivity reaction.
- Any other ≥ Grade 3 non-skin related adverse event with the exception of events listed under "No Discontinuation" (below).
- Any ≥ Grade 4 laboratory abnormalities, except AST, ALT, or Total Bilirubin
- AST or ALT > 8 x ULN
- Total Bilirubin > 5 x ULN
- Any other ≥ Grade 4 adverse event
- Any adverse event, laboratory abnormality or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the patient with continued dosing.
- The development of progression (irPD) in the global tumor burden confirmed by serial imaging 4-6 weeks later and/or clinical deterioration of subject's condition such that further benefit from ipilimumab dosing is unlikely or requires a change of therapy.

Please refer to the IB for specific treatment algorithms.

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

- Any motor neurologic toxicity >/= Grade 3 regardless of causality [redacted]

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- Any>/= Grade 3 treatment related sensory neurologic toxicity

Please refer to the IB for specific treatment algorithms.

5.1.5.b 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 CTLA4 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,

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appropriate work-up (including biopsy if possible) should be performed, and steroid therapy may be considered if clinically necessary. .

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

Specific treatment algorithms for immune-related adverse events are included as appendices in the IB.

5.1.7 Other Guidance

5.1.7.a 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 premedication 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.

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- 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.b 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

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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.

5.1.7.c Liver Function Tests (LFT) Assessments Required Prior to Administration of ipilimumab

Liver function tests (AST, ALT, T. bilirubin) will be evaluated for every subject prior to administration of ipilimumab. Blood samples must be collected and analyzed at local or central labs within 3 days prior to dosing. LFT results must be reviewed by the principal investigator (or designee) to meet dosing criteria specifications: $\leq$ 2.5 x ULN for AST, ALT and $\leq$ 2.0 x ULN for T. bilirubin unless liver metastases are present in which case LFT $\leq$ 5 x ULN for AST, ALT and T. bilirubin $\leq$ 3.0 x ULN) prior to dosing.

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

5.2 Interleukin-2 (IL-2; Aldesleukin; Proleukin)

IL-2 will be given intravenously (IV) in a dose of 600,000 IU/kg every eight hours for up to 14 doses in each cycle. Cycles of IL-2 will be repeated in 3 weeks with the next dose of ipilimumab.

Dose Calculations of IL-2

Calculate Total Dose as follows: Patient body weight in kg X [600,000 MIU] = total dose in MIU

Calculate Rate of Infusion as follows: Infusion volume in ml ÷ 15 minutes=rate of infusion in ml/min

5.2.1 Storage, Preparation, and Administration of IL-2

Reconstituted IL-2 should be further diluted with 5% Dextrose, USP. Do not mix with saline containing solutions. Reconstituted IL-2 may be diluted as necessary in volumes of 50 ml to 500 ml with 5% Dextrose, USP. When diluted for IV administration in 5% Dextrose Injection, USP, in a plastic bag (e.g. Viaflex, manufactured by Travenol Laboratories, Inc.,) IL-2 is chemically stable for 48 hours at refrigerated and room temperatures, 2-30°C. Intact vials are stored in the refrigerator (2-8°C) protected from light. Each vial bears an expiration date.

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5.2.2 IL-2 Formulation/Reconstitution: IL-2 (Aldesleukin®)

Formulation/Reconstitution: IL-2 (Aldesleukin®), please see the Investigators Brochure for the complete pharmaceutical package insert) is a commercially available product (Prometheus).

1)The medication is provided as a lyophilized powder and a vial of medication is reconstituted with 1.2mg of Sterile Water for Injection, USP, and the resultant concentration is 18 million IU/ml.

2)Diluent should be directed against the side of the vile to avoid excess foaming. Swirl contents gently until completely resolved.

3)Do not shake.

Since vials contain no preservative, reconstituted solution should be used within 8 hours.

5.2.3 Dose Modifications of IL-2

No dose modifications will be allowed. However, based on principle investigator's discretion, dose can be calculated using the ideal body weight. If DLT occurs, dose delays will be administered according to investigators judgment. When DLT has resolved, the patient may be continued at the same dose of IL-2 or may be withdrawn from treatment with IL-2.

For IL-2, serious adverse events are defined as any of the following:

- Any grade 3 or greater non-hematological toxicity, with the exceptions of grade 3 arthralgia/myalgias and brief (less than 1 week) grade 3 fatigue.
- Hypotension with systolic BP<80 and not responsive to fluid resuscitation or vasopressors
- Pulmonary edema requiring treatment with Lasix.
- Any cardiac arrhythmia or sinus tachycardia> 130 bpm
- Severe altered mental status
- Elevation of creatinine (>4 .0 mg/dl, hold dose, >8 mg/dl, stop treatment)
- Elevated total bilirubin (>3.7 mg/dl, consider holding dose, 7.5 mg/dl, consider stopping therapy)
- Low platelet count (<75 k/ul, hold dose, <50 k/ul, consider stopping therapy)

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Common and expected toxicities related to IL-2 administration will not be considered reportable adverse events except for autoimmune events or the treating clinical investigator believes that ipilimumab contributed to the development of the adverse event.

In the event that a patient is experiencing a significant ipilimumab-related adverse event at the time that IL-2 is scheduled, the IL-2 may be held until the ipilimumab-related adverse event resolves. IL-2 may be given at the next regularly scheduled 3 week cycle. In general, if the following ipilimumab-related adverse events are present at the time of a scheduled IL-2 treatment, the IL-2 should be held:

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

If these adverse events resolve to Grade 1 or less within three weeks, IL-2 can be given at the next regularly scheduled cycle of treatment. If there are questions about a specific patient, the investigator may contact the study PI and/or BMS for further discussion.

5.2.4 Definitions of IL-2 Dose-Limiting Toxicity

Toxicity will be evaluated according to the NCI Common Toxicity Criteria, CTCAE v4.0. Common and expected toxicities related to HD IL-2 administration will not be considered reportable adverse events unless ipilimumab contributed to the development of the adverse event in the judgment of the treating clinician. IL-2 related side effects are vary in incidence and intensity mainly as results of capillary leak syndrome (CLS), the leakage of intravascular fluid to the extra vascular space, subcutaneous tissue or alveoli [78]. CLS causes hypotension, pulmonary and peripheral edema, significant weight gain, altered mental status, tachycardia and oliguria. These symptoms usually resolve within 24-48 hours of following treatment cessation with an exception of fatigue which can persist for 5-7 days post discharge.

IL-2 will be permanently discontinued for any grade ≥ 4 hematological or ≥ 3 non-hematological adverse events that do not resolve to ≤ grade [redacted]

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completing IL-2 treatment if the side effect is definitely related to IL-2. This will be considered a DLT and the patient will be removed from the study.

5.3 Prohibited and Restricted Therapies During the Study

5.3.1 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
- Immunosuppressive agents
- 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).

5.3.2 Restricted Therapies

Patients should avoid beta-blockers while on this protocol since these agents may preclude successful treatment of IL-2-related hypotension. Patients may be weaned off of beta-blockers two weeks prior to study enrollment under the supervision of their primary cardiologist.

5.3.3 Precautions

Caution is advised when treating patients with high-dose IL-2 who have previously been administered ipilimumab, particularly in patients who experienced ipilimumab-related diarrhea/colitis. Colonoscopy or sigmoidoscopy with biopsy may be advisable in these patients prior to IL-2 administration.

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6. STUDY PROCEDURES AND OBSERVATIONS

6.1 Time and Events Schedule

All patients must give written consent to participate in the study. A total of 11 visits are planned including one pre-visit, up to eight treatment visits and 4 follow-up visits at 6, 9, 12 and 24 months. Time and events schedule is summarized in Table 5.

Table 5: Time and events schedule for the protocol

Procedure	Screening	Induction				Induction Assessment	Maintenance				End of Treatment	L
	Pre-Treatment	Tx1	Tx2	Tx3	Tx4	F/U 1	Tx 5 F/U 2	Tx 6 F/U 3	Tx 7 F/U4	Tx 8 F/U5	F/U 6	
Weeks (±1)[a]:	-2	1	4	7	10	12	24	36	48	60	104	
Months		1				3	6	9	12	24	36	
Eligibility Assessments												
Informed Consent	X											
Inclusion/Exclusion Criteria	X						X					
Medical History	X					X	X	X	X	X	X	
Safety Assessments												
Physical Examination	X					X	X	X	X	X	X	
Targeted Physical Exam		X	X	X	X							
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs (including height and weight)[b]	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events Assessment/Con Meds		X	X	X	X	X	X	X	X	X		
Laboratory Tests[1]	X		X	X	X		X	X	X	X	X	
Urinalysis	X		X	X								
Pregnancy Test[2]	X		X	X	X		X	X	X	X		
EKG	X		x	x								
Cardiac Stress Test	X											
Pulmonary Function Test(if needed)[7]	X											
Efficacy Assessments												

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Assessment 1 (safety)	X	X	X	X	X	X	X	X	X	X	X	
Assessment 2 (Imaging) (efficacy)[3]	X					X	X	X	X	X	X	
Assessment 3 (Immunology)[4]	X	X	X	X		X	X			X	X	
Tissue collection(optional)[5]	X						X				X	
Study Treatment												
IL-2			X	X								
Ipilimumab		X	X	X	X		X	X	X	X		

Abbreviations: F/U, follow-up; IL2, interleukin-2; Ipi, ipilumimab; Tx, treatment visit

[a]Pre-treatment imaging, informed consent, H&P, cardiac stress test, pulmonary functions studies(if needed), concomitant medications and tumor biopsy must be completed within 4 weeks of starting treatment. Vital signs, routine labs, EKG must be completed within 2 weeks of starting treatment. Pregnancy testing, if needed, must be done within 72 hours of starting treatment. Follow-up imaging must be done within 1 week of scheduled follow-up visit.

[b]Vital signs should include temperature, heart rate, respirations, blood pressure, height and weight at each visit.

[1]Routine lab tests include cbc with differential, serum electrolytes, BUN creatinine, glucose, hepatic function studies (bilirubin, AST, ALT), LDH, , T3, T4 and TSH prior to treatment;;

[1a] pre- IL-2 standard tests: Urinalysis and EKG prior to IL-2. Patients must also have institutionally mandated pre-IL-2 studies, such as cardiac stress test, pulmonary function studies.

[2]Pregnancy test must be done in all women of reproductive potential and subjects should be counseled in avoiding pregnancy during treatment as outlined in Section 4. For woman of child-bearing potential, a negative result must be confirmed within 24 hours of each dose of ipilimumab. The test should be repeated at week 24 in pre-menopausal women prior to beginning maintenance ipilimumab treatment. Women under the age of 62 must have a documented serum follicle stimulating hormone, (FSH) level > 40mIU/mL

[3]Patients should have a CT scan of the chest, abdomen and pelvis with and without contrast and CT or MRI of the brain within 4 weeks of starting treatment and during efficacy assessment weeks. Additional imaging may be done at the investigators discretion to better evaluate disease (e.g. CT/MRI of the lower extremity for soft tissue disease, PET or bone scan for borderline lesions).

[4]Peripheral blood will be collected for immune analysis at the indicated time points. This will include 4 green or red CPT tubes and 2 red top tubes. Blood will be shipped to the central immunology lab as described in Section 12.1.

[5]In consenting patients with easily accessible disease a tumor biopsy will be performed at the indicated time points. An incisional, excisional or core needle biopsy is acceptable. Tissue should be sent to the central immunology lab as described in Section 12.1.. Biopsy is optional and archival tissue is acceptable for the pre-treatment sample.

[6] Long term survival follow up will be conducted by phone if patient is unable to come to clinic.

[7] Pulmonary Function: FEV1 and FVC > 65% of prediction for those patients with extensive pulmonary metastases or chronic pulmonary disease history.

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6.2 Procedures by Visit

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

6.2.1 Study Procedures by Visit and Treatment Cycle

Note that results of all safety laboratory tests (that is, all chemistry and all hematology results) must be obtained and reviewed before ipilimumab administration, as applicable. All laboratory results must be within the established range before ipilimumab is administered. All induction period laboratory samples must be collected within a window of up to 7 days before administration of ipilimumab. Laboratory evaluations using a local laboratory must be performed and the result examined by the investigator before administration of each dose of ipilimumab.

6.2.2 Screening/Baseline Visit

Once informed consent has been obtained, the tests described in Table 6 will be performed. All tests must be conducted within two weeks prior to starting treatment, with the exception of CT scans of the, chest/ abdomen/ pelvis areas and CT or MRI of the Brain, which may be done up to four weeks before the first treatment. After giving fully informed consent, patients will be subjected to a medical history and physical examination to document general fitness to proceed with the trial. The diagnosis should be confirmed histologically from the patient's record. Peripheral blood will be drawn and shipped to the tumor immunology lab for a baseline sample, and shipped to the central tumor immunology lab as described in Section 12.1. If possible, and the patient consents, biopsy samples preferably will be taken and sent to the tumor immunology laboratory as described in Section 12.1. Samples will be assessed at baseline, during and post-treatment periods. Metastases will be documented using relevant CT scans (chest, abdomen, and pelvis ww/out contrast). An MRI scan of the brain will be obtained. A cardiac stress test and pulmonary function tests will be obtained in appropriate patients before IL-2 as per institutional guidelines.

Table 6: Pretreatment evaluations for all groups

Medical History Physical Exam	≤4 weeks	☐ Cardiac Stress Test ☐ Pulmonary Function Test. (optional) ☐ Medical History including ☐ Concomitant Medications Physical Examination
Diagnostic imaging	≤4 weeks	☐ Brain MRI or CT ☐ CT scan (chest abdomen and pelvis w/wout contrast)

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Inclusion/exclusion criteria, Medical History, and Physical Examination,	≤2 weeks	☐ Height ☐ Weight ☐ Blood, pressure (sitting) / pulse (resting) ☐ ECOG performance status ☐ EKG
Serum pregnancy, (if applicable)	≤72 hours	HCG
Hematology	≤2 weeks	☐ Complete Blood Count (CBC), ☐ Differential, Platelets
Biochemistry	≤2 weeks	☐ Electrolytes (sodium, potassium, calcium, chloride and magnesium), ☐ Alanine aminotransferase (ALT) and/or aspartate Aminotransferase (AST), ☐ Alkaline phosphatase (ALP), ☐ Total bilirubin, ☐ Serum creatinine, ☐ Blood urea nitrogen (BUN), ☐ Serum protein, ☐ Albumin, ☐ Lactic dehydrogenase (LDH), ☐ T3, ☐ T4, ☐ Thyroid stimulating hormone (TSH)
Urinalysis	≤2 weeks	☐ Protein, ☐ WBC, ☐ RBC, Glucose
Tumor biopsy (optional)*	≤2 weeks	mmunohistochemistry, confocal microscopic study and immunophenotypes of T subsets mmunohistochemistry and confocal microscopy analysis of tumor microenvironment
Immunologic Monitoring	≤2 weeks	mmunophenotypes for Tregs Dextramer, tetramer and/or ELISPOT assay, to enumerate antigen-specific cytokine secreting T-cells HC and confocal staining for tumor antigens and Tregs and Ts, MDSC in the tumor microenvironment

*Only patients who qualify for entry into the study and consent to the procedure will have a tumor biopsy (prior to study). Studies will include immunohistochemistry and confocal microscopy, ex vivo analysis of base line tumor infiltrating lymphocytes for pre-existing anti-tumor immune response and to compare with post-treatment samples.

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