Dana-Farber Cancer Institute
Dana-Farber/Harvard Cancer Center

A Phase I Trial of Bevacizumab plus Ipilimumab in Patients with Unresectable Stage III or Stage IV Melanoma

Study Drugs:
Bevacizumab
Ipilimumab

Support Provided By
Genentech, Inc.
Bristol-Myers Squibb

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SYNOPSIS

Title of Study: BMS Protocol Number CA184058/Genentech AVF 4122s: A Phase I Trial of Bevacizumab plus Ipilimumab in Patients with Unresectable Stage III or Stage IV Melanoma

Estimated Number of Study Centers and Countries/Regions: 1

Study Phase: I

Research Hypothesis: The observation of the vascular effects of ipilimumab on tumor deposits further supports the critical importance of angiogenesis to tumor growth. The clinical efficacy of targeting VEGF and its effect on pathologic angiogenesis has been extensively studied with the use of bevacizumab. Given the profound effects on tumor vasculature witnessed in melanoma patients being treated with ipilimumab and the known effects of bevacizumab, we propose a phase I study testing the combination of these two drugs in patients with metastatic melanoma.

Primary Objective:

To determine the safety, tolerability and maximum tolerated dosing for the combination of bevacizumab plus ipilimumab in patients with unresectable stage III or stage IV melanoma

Secondary Objectives

To determine best overall response rate by standard solid tumor response criteria, time to progression, disease control rate, and the duration of response for the combination of bevacizumab plus ipilimumab in patients with unresectable stage III or stage IV melanoma

To perform correlative studies investigating the effects of this combination therapy on anti-tumor immunity and tumor vasculature.

To gain additional experience with the combination using 3mg/kg ipilimumab dosing plus bevacizumab.

Study Design:

Cohort 1: Ipilimumab 10 mg/kg IV doses every 3 weeks x 4 doses (induction), then every 3 months (maintenance); Bevacizumab 7.5 mg/kg IV every 3 weeks (continuous)

Cohort 2: Ipilimumab 10 mg/kg IV doses every 3 weeks x 4 doses (induction), then every 3 months (maintenance); Bevacizumab 15 mg/kg IV every 3 weeks (continuous)

Cohort 3: Ipilimumab 3 mg/kg IV doses every 3 weeks x 4 doses (induction), then every 3 months (maintenance); Bevacizumab 7.5 mg/kg IV every 3 weeks (continuous)

Cohort 4: Ipilimumab 3 mg/kg IV doses every 3 weeks x 4 doses (induction), then every 3 months (maintenance); Bevacizumab 15 mg/kg IV every 3 weeks (continuous)

The primary goal of the correlative sciences is to obtain an early gauge of anti-cancer immunological activity and effects on the tumor vasculature of the combination of bevacizumab and ipilimumab.

Duration of Study: < 2 years

Number of Subjects: 6 total patients

Study Population: Over the age of 18 with Stage IV or unresectable Stage III metastatic melanoma

Test Product, Dose and Mode of Administration, Duration of Treatment: Ipilimumab (BMS-734016) formerly referred to as MDX-010.

Cohort 1: Ipilimumab 10 mg/kg IV every 3 weeks x 4 doses (induction), then every 3 months (maintenance); Bevacizumab 7.5 mg/kg IV every 3 weeks (continuous)

Cohort 2: Ipilimumab 10 mg/kg IV every 3 weeks x 4 doses(induction), then every 3 months (maintenance); Bevacizumab 15 mg/kg IV every 3 weeks (continuous)

Cohort 3: Ipilimumab 3 mg/kg IV every 3 weeks x 4 doses (induction), then every 3 months (maintenance); Bevacizumab 7.5 mg/kg IV every 3 weeks (continuous)

Cohort 4: Ipilimumab 3 mg/kg IV every 3 weeks x 4 doses (induction), then every 3 months (maintenance); Bevacizumab 15 mg/kg IV every 3 weeks (continuous)

Reference Therapy, Dose and Mode of Administration, Duration of Treatment: Bevacizumab plus Ipilimumab

Patients will be staged every 3 months. Patients may continue treatment if there is evidence for stable or responsive disease by RECIST criteria. Experience with ipilimumab has proven that target lesions following treatment that enlarge radiographically may have evidence for tumor destruction and inflammation on histologic examination. Many months of treatment may be necessary until a response by traditional RECIST criteria are met, yet these patients are likely receiving benefit from such treatment. As a result, patients with up to 40% increase in the sum of the longest diameter and patients having no more than 2 new target lesions may continue with treatment. Evaluations by standard response criteria will still be recorded for these patients.

Criteria for Evaluation

Safety Measures: Safety will be evaluated for all treated patients using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events v3.0 (CTCAE). Safety assessments will be based on medical review of AE reports and the results of vital sign measurements, physical examinations and clinical laboratory tests. The incidence of AEs will be tabulated and reviewed for potential significance and clinical importance. The reporting period for safety data will be from the date of first on-study dose to 70 days after the last dose is received. Additionally, from the time of consent forward, any occurrence of a serious adverse event (SAE) must be reported to company sponsors Genentech and BMS.

Statistical Methods:

A patient will be classified as having a DLT for any of the following:

- An unexpected toxicity of grade 3 or higher,
- A toxicity of grade 3 or higher outlined in the Dose Modification and Toxicity Management section of this protocol that is not effectively managed with local or systemic immunosuppression within 7 days
- Eye pain of grade 2 or higher, or uveitis of any grade
- A immunological toxicity of grade 4 related to ipilimumab
- Two delays of treatment (not due to scheduling non-compliance) each lasting more than 10 days within 4 cycles of drug.

Patients will enter each cohort in sets of five, beginning in Cohort 1, and receive four cycles of study drug. For determination of DLT, treatment length is 12 weeks. If three or more patients experience dose-limiting toxicity (DLT) during the first 12 weeks, Cohort 1 will be determined to have unacceptable toxicity. The next set of five patients will then be enrolled in Cohort 3, which will maintain the dosage of bevacizumab and decrease ipilimumab to 3.0 mg/kg. Enrollment into Cohort 3 will require discussion between the Principal Investigator and Bristol-Myers Squibb (BMS) and written approval from a BMS representative. If there are three or more patients with DLT during the first 12 weeks in Cohort 3, the study will be halted pending further discussion with BMS. Otherwise, the study will continue and enroll the next five patients into Cohort 4, increasing the dose of bevacizumab. If there are three or more patients with DLT in Cohort 4, then Cohort 3 will be the MTD. If the toxicity profile of Cohort 4 is acceptable, it will be the MTD.

If the toxicity profile of Cohort 1 is acceptable, the next set of five patients will be enrolled into Cohort 2, testing the combined effect of both bevacizumab and ipilimumab at high dose levels. If three or more patients experience DLT during the first 12 weeks, Cohort 2 will be determined to have unacceptable toxicity and Cohort 1 will be considered the MTD. Otherwise, the MTD will be Cohort 2.

Progression to either Cohort 2 or Cohort 3 will depend solely upon the toxicity profile observed in Cohort 1; there will be no escalation from Cohort 2 to Cohort 3.

Before escalation to the next dose level, three patients in a cohort must complete the 12 weeks of induction treatment without dose limiting toxicities.

Patients in any cohort exhibiting DLT will not be replaced; however, up to two patients may be replaced in a cohort due to rapid progression of disease within the first four weeks that requires alternative treatment. These patients will not be considered to have a DLT, but will be included in the determination of secondary endpoints.

To ensure that toxicity at the MTD is acceptable and to gain preliminary experience with biologic activity of the two drugs, an additional 12 patients will be accrued at the MTD. The operating characteristics of this design are shown in Table 1.

Table 1 – Probability of Escalation

True (but Unknown) Rate of DLT (%)	Probability of Escalation (%)
5	99.9
10	99.1
20	94.2
30	83.7
40	68.2
50	50.0
60	31.7
70	16.3

Under this design, there is a 94% probability of escalation if the true rate of DLT is no more than 20%. If the true rate of DLT exceeds 50%, the probability of escalation is less than 50%.

As an amendment to this protocol, 12 patients will be enrolled to each of two cohorts that will treat with ipilimumab at 3 mg/kg, the dose of ipilimumab that was found to provide statistically significant increases in overall survival (Hodi et al.NEJM). Ipilimumab will be combined with 7.5 mg/kg of bevacizumab in the first cohort, and with 15 mg/kg bevacizumab in the second cohort. Secondary and correlative study endpoints will be assessed for these cohorts in addition to the cohort of patients treated at the MTD.

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1.0 BACKGROUND

1.1 DISEASE BACKGROUND

In the United States in 2003, malignant melanoma was diagnosed in 54,200 patients and was the cause the death in 7,700(1). The disease will account for 4% of all new cancers and 1.4% of all cancer deaths. The neoplasm will be the second and third most frequently diagnosed cancer from birth to age 39 in females and males, respectively. Moreover, with an annual incidence increasing at 4% per year, the largest of any cancer type, an individual's lifetime risk for developing melanoma is currently greater than 1 in 65(2).

Surgical excision is curative for most patients who present with relatively thin lesions (<1.0 mm)(3). Those with melanoma limited to the primary site show a ten-year survival ranging from 60-90%, with the prognosis most strongly correlated with the primary tumor thickness(4). For patients with lymph node metastases, adjuvant therapy with α-interferon affords a modest increase in overall survival, but this advantage is associated with substantial toxicities(5-8). For patients with metastatic disease, there is little convincing evidence that any standard systemic therapy prolongs life. Dacarbazine is the most active single agent for disseminated disease, but complete responses are infrequent and of short duration(9). Whereas bleomycin, cisplatin, BCNU, carboplatin, taxol, navelbine, gemcitabine, tamoxifen, and vinblastine, singly or in combination, may induce occasional tumor regressions, these regimens are toxic and fail to augment survival. Similarly, high dose chemotherapy with autologous bone marrow support offers no meaningful clinical benefit.

1.2 BEVACIZUMAB CLINICAL EXPERIENCE

Bevacizumab has been studied in a multitude of Phase I, II, and III clinical trials in more than 5000 patients and in multiple tumor types. The following discussion summarizes bevacizumab's safety profile and presents some of the efficacy results pertinent to this particular trial. Please refer to the bevacizumab Investigator Brochure for descriptions of all completed Phase I, II, and III trials reported to date.

In a large phase III study (AVF2107g) in patients with metastatic colorectal cancer, the addition of bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF), to irinotecan/5-fluorouracil/leucovorin (IFL) chemotherapy resulted in a clinically and statistically significant increase in duration of survival, with a hazard ratio of death of 0.67 (median survival 15.6 vs. 20.3months; $p<0.001$). Similar increases were seen in progression-free survival (6.2 vs. 10.6 months; $p<0.001$), overall response rate (35% vs. 45%; $p<0.01$) and duration of response (7.1vs. 10.4 months; $p<0.01$) for the combination arm versus the chemotherapy only arm (bevacizumab Investigator Brochure, October 2005).

Based on the survival advantage demonstrated in Study AVF2107g, bevacizumab was designated for priority review and was approved on 26 February 2004 in the United States for first-line treatment in combination with IV 5-FU–based chemotherapy for subjects with metastatic colorectal cancer.

Pharmacokinetic data with 5 mg/kg every 2 weeks shows comparability with 7.5 mg every three weeks and 10 mg/kg every 2 weeks is comparable to 15 mg/kg every 3 weeks.

a. Safety Profile

In the initial Phase I and II clinical trials, four potential bevacizumab-associated safety signals were identified: hypertension, proteinuria, thromboembolic events, and hemorrhage. Additional completed Phase II and Phase III studies of bevacizumab as well as spontaneous reports have further defined the safety profile of this agent. Bevacizumab-associated adverse events identified in phase III trials include congestive heart failure (CHF), gastrointestinal perforations, wound healing complications, and arterial thromboembolic events (ATE). These and other safety signals are described in further detail as follows and in the bevacizumab Investigator Brochure.

Hypertension: Hypertension has been commonly seen in bevacizumab clinical trials to date and oral medications have been used to manage the hypertension when indicated. Grade 4 and 5 hypertensive events are rare. Clinical sequelae of hypertension are rare but have included hypertensive crisis, hypertensive encephalopathy, and reversible posterior

leukoencephalopathy syndrome (RPLS)(10, 11). RPLS may include signs and symptoms of headache, altered mental function, seizures, and visual disturbances / cortical blindness and requires treatment, which should include control of hypertension, management of specific symptoms, and discontinuation of bevacizumab.

Proteinuria: Proteinuria has been commonly seen in bevacizumab clinical trials to date. The severity of proteinuria has ranged from asymptomatic and transient events detected on routine dipstick urinalysis to nephrotic syndrome; the majority of proteinuria events have been grade 1 or 2. In study AVF2107g, none of the 118 patients receiving bolus-IFL plus placebo, three of 158 patients (2%) receiving bolus-IFL plus bevacizumab, and two of 50 (4%) patients receiving 5-FU/LV plus bevacizumab who had a 24-hour collection experienced grade 3 proteinuria (> 3.5 g protein/24 hr). Rare events of nephrotic syndrome have occurred, and bevacizumab should be discontinued in patients with nephrotic syndrome.

Thromboembolic Events: Both venous and arterial thromboembolic (TE) events, ranging in severity from catheter-associated phlebitis to fatal, have been reported in patients treated with bevacizumab in the colorectal cancer trials and, to a lesser extent, in patients treated with bevacizumab in NSCLC and breast cancer trials. In the phase III pivotal trial in metastatic CRC, there was a slightly higher rate of **venous TE** events that was not statistically significant in patients treated with bevacizumab plus chemotherapy compared with chemotherapy alone (19% vs. 16%). There was also a higher rate of **arterial TE** events (3% vs. 1%) such as myocardial infarction, transient ischemia attack, cerebrovascular accident/stroke and angina/unstable angina**.** A pooled analysis of the rate of arterial TE events from 5 randomized studies (1745 patients) showed that treatment with chemotherapy plus bevacizumab increased the risk of having an arterial TE event compared with chemotherapy alone (3.8% vs. 1.7%, respectively) (Skillings et al., 2005). Furthermore, subjects with certain baseline characteristics (age ≥ 65 years and/or a history of a prior arterial TE event) may be at higher risk of experiencing such an event. See the bevacizumab Investigator Brochure for additional information on risk factors.

Aspirin is a standard therapy for primary and secondary prophylaxis of arterial thromboembolic events in patients at high risk of such events, and the use of aspirin ≤ 325 mg daily was allowed in the five randomized studies discussed above. Use of aspirin

was assessed routinely as a baseline or concomitant medication in these trials, though safety analyses specifically regarding aspirin use were not preplanned. Due to the relatively small numbers of aspirin users and arterial thromboembolic events, retrospective analyses of the ability of aspirin to affect the risk of such events were inconclusive. However, similarly retrospective analyses suggested that the use of up to 325 mg of aspirin daily does not increase the risk of grade 1-2 or grade 3-4 bleeding events, and similar data with respect to metastatic colorectal cancer patients were presented at ASCO 2005 (Hambleton et al., 2005). Further analyses of the effects of concomitant use of bevacizumab and aspirin in colorectal and other tumor types are ongoing.

Gastrointestinal perforation Patients with metastatic carcinoma may be at increased risk for the development of gastrointestinal perforation when treated with bevacizumab and chemotherapy. Bevacizumab should be permanently discontinued in patients who develop gastrointestinal perforation. A causal association of intra-abdominal inflammatory process and gastrointestinal perforation to bevacizumab has not been established. Nevertheless, caution should be exercised when treating patients with intra-abdominal inflammatory processes with bevacizumab. Gastrointestinal perforation has been reported in other trials in non-colorectal cancer populations (e.g., ovarian, renal cell, pancreas, and breast) and may be higher in incidence in some tumor types.

Wound healing complications: Wound healing complications such as wound dehiscence have been reported in patients receiving bevacizumab. In an analysis of pooled data from two trials in metastatic colorectal cancer, patients undergoing surgery 28-60 days before study treatment with 5-FU/LV plus bevacizumab did not appear to have an increased risk of wound healing complications compared to those treated with chemotherapy alone(12). Surgery in patients currently receiving bevacizumab is not recommended. No definitive data are available to define a safe interval after bevacizumab exposure with respect to wound healing risk in patients receiving elective surgery; however, the estimated half life of bevacizumab is 20 days. Bevacizumab should be discontinued in patients with severe wound healing complications.

Hemorrhage: Overall, grade 3 and 4 bleeding events were observed in 4.0% of 1132 patients treated with bevacizumab in a pooled database from eight phase I, II, and III

clinical trials in multiple tumor types (bevacizumab Investigator Brochure, October 2005). The hemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumor-associated hemorrhage (see below) and minor mucocutaneous hemorrhage.

Tumor-associated hemorrhage was observed in phase I and phase II bevacizumab studies. Six serious events, of which 4 had fatal outcome, were observed in a phase II trial of patients with non-small cell lung cancer receiving bevacizumab. These events occurred suddenly and presented as major or massive hemoptysis in patients with either squamous cell histology and/or tumors located in the center of the chest in close proximity to major blood vessels. In five of these cases, these hemorrhages were preceded by cavitation and/or necrosis of the tumor. Tumor-associated hemorrhage was also seen rarely in other tumor types and locations, including central nervous system (CNS) bleeding in a patient with hepatoma with occult CNS metastases and continuous oozing of blood from a thigh sarcoma with necrosis.

Across all bevacizumab clinical trials, mucocutaneous hemorrhage has been seen in 20%-40% of patients treated with bevacizumab. These were most commonly grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes in bevacizumab treatment regimen. There have also been less common events of minor mucocutaneous hemorrhage in other locations, such as gingival bleeding and vaginal bleeding.

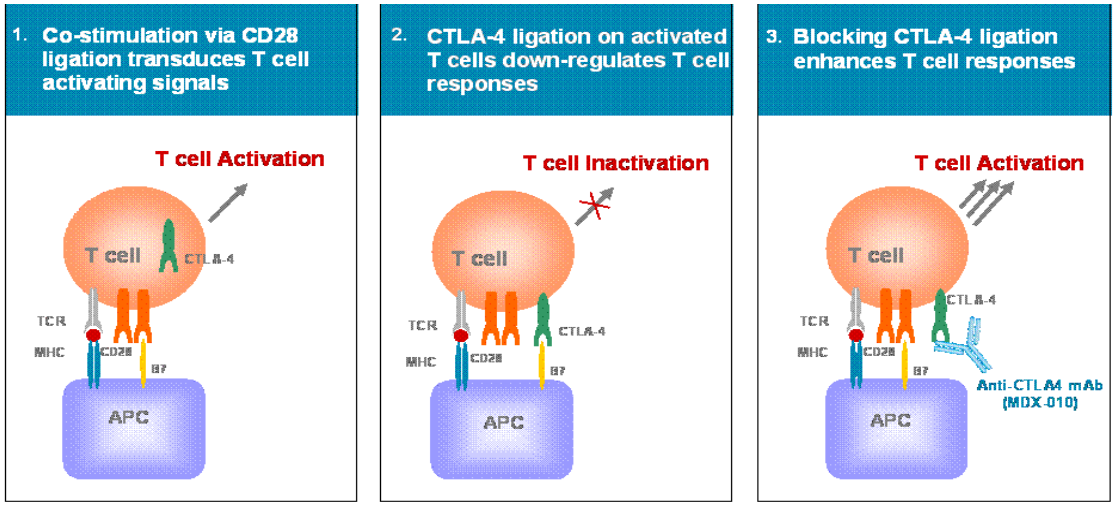
Congestive heart failure: CHF has been reported in bevacizumab clinical trials and may be increased in incidence in patients with prior exposure to anthracyclines or prior irradiation to the chest wall. In a phase III trial (AVF2119g) of capecitabine with or without bevacizumab for metastatic breast cancer, 7 subjects (3.1%) who received capecitabine plus bevacizumab developed clinically significant CHF compared with 2 subjects (0.9%) treated with capecitabine alone; of note, all subjects in this trial had had prior anthracycline treatment. In addition, 2 subjects had a left ventricular ejection fraction < 50% at baseline and 2 others had prior left chest wall irradiation. A recently published phase II study in subjects with refractory acute myelogenous leukemia reported 5 cases of cardiac dysfunction (CHF or decreases to <40% in left ventricular ejection fraction) of 48 subjects treated with sequential cytarabine, mitoxantrone, and

bevacizumab. All but one of these subjects had significant prior exposure to anthracyclines as well(13). Other studies are ongoing in this patient population. Patients receiving anthracyclines or with prior exposure to anthracyclines should have a baseline MUGA or ECHO with a normal ejection fraction.

ADDITIONAL ADVERSE EVENTS: SEE THE BEVACIZUMAB INVESTIGATOR BROCHURE FOR ADDITIONAL DETAILS REGARDING THE SAFETY EXPERIENCE WITH BEVACIZUMAB.1.3 IPILIMUMAB BACKGROUNDRESEARCH HYPOTHESIS AND PRODUCT DEVELOPMENT RATIONALE

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)(14). Refer to Figure. Expression of B7 has been shown to be limited to “professional” antigen presenting cells; that is, specialized cells of the hematopoietic lineage, including

dendritic cells, activated macrophages, and activated B cells. It has been suggested that this sharply-defined restriction of B7 expression is a fail-safe mechanism for maintenance of peripheral T cell tolerance, insuring that T cell activation can only be stimulated by appropriate APCs(15). The fact that tumor cells do not express B7 contributes to their poor capacity to elicit immune responses(16, 17). The demonstration that induction of expression of B7 on many tumor cells by transfection, transduction, or other mechanisms can heighten tumor immunogenicity led to great interest in pursuing this as an approach to tumor immunotherapy. As demonstrated in vivo in murine tumor models, the utility of B7 expression as a vaccination approach is limited by the following factors: (1) B7-expressing tumor cell vaccines are only effective when the tumor cells have a high degree of inherent immunogenicity; (2) while B7-expressing vaccines have been shown in many cases to be effective in inducing protective immune responses, they have demonstrated only limited utility in inducing responses to established tumors; and (3) inactivation of tumor cells by radiation has been shown to destroy the immuno-enhancing activity of the B7 gene product(18, 19).

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(20). 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(21). 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(22-25). Blocking CTLA-4-B7 interaction while preserving signaling via CD28 resulted in enhanced T cell responses in vitro.

Perhaps the most convincing demonstration of the down-regulatory role of CTLA-4 came from examination of mice with a null mutation(26-28). CTLA-4 knockout mice appear to have spontaneously activated T cells evident at approximately 1 week after birth, followed by rampant lymphoproliferation and lymphadenopathy. These mice die at approximately 3 weeks of age, either as a result of polyclonal T cell expansion and tissue destruction or as a result of toxic shock resulting from lymphokine production by the T cells. Since thymocyte differentiation and selection proceed normally in CTLA-4-deficient mice, the rampant T cell expansion that occurs in the mice indicates that CTLA-4 plays a critical role in down-regulating T cell responses in the periphery.

Summary of Results of Investigational Program

Pharmacology

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.

Pre-Clinical Toxicology

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 PHA- or (CD)3-activated human T cells. However, low to moderate ADCC activity was noted at concentrations up to 50 μg/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.

Summary of pre-clinical pharmacology data for ipilimumab

Please refer to the latest Investigator Brochure for full summary information on the development of ipilimumab.

In vivo evaluation of anti-murine CTLA-4 mAb in mouse tumor models

In murine tumor models, anti-CTLA-4 mAb treatment alone significantly inhibited growth of inherently immunogenic tumors. This included models where the compound was administered after tumor implantation followed by a prolonged period of growth that allowed the tumors to reach a size of approximately 150 mm^2. Furthermore, in combination with vaccine therapy, anti-CTLA-4 mAb treatment effectively inhibited growth of non-immunogenic tumors.

One model worth noting is the B16 Melanoma model which is an extremely aggressive tumor model, characterized by a very low lethal dose (LD50) and high capacity for metastasis. In this model, anti-CTLA-4 mAb blockade, or treatment with irradiated parental B16 cells or granulocyte-macrophage colony stimulating factor (GM-CSF) transfected B16 (GM-B16) cells, showed minimal or no effect on inducing tumor rejection. In marked contrast, treatment with the combination of anti-CTLA-4 mAb and irradiated GM-B16 cells at the time of tumor inoculation prevented outgrowth of tumors in virtually all mice. Moreover, combination therapy was capable of protecting mice from death due to pulmonary metastases induced by intravenous injection of B16 sub line F10.

In vivo evaluation of ipilimumab in mouse tumor models

Tumor rejection of MC38 murine colorectal adenocarcinoma cells was evaluated in a mouse strain that was engineered to express human CTLA-4 in mouse T cells but not the mouse orthologue. Ipilimumab rejection of the MC38 tumor cells, while an anti-mouse CTLA-4

antibody, was unsuccessful. This study provides evidence that ipilimumab can elicit an effective antitumor immune response in vivo.

In vivo evaluation of ipilimumab in Cynomolgus Monkeys

Antibody response to vaccines in the presence and absence of ipilimumab was evaluated in cynomolgus monkeys. The outcome of two independent studies employing two different vaccines demonstrated statistically significant increases in antigen-specific antibody responses. In one study, a 4 to 5 fold increase over control was demonstrated with a student's t-test of $P < 0.05$ at 7 weeks and $P < 0.01$ at 9 weeks. In the second study, a statistically significant increase in the humoral immune response was demonstrated by 41 days and remained elevated throughout the study. Of note, the durability of the immune response after 1 or more doses of ipilimumab in animals and humans is under investigation.

Clinical Safety Data to Date

Ipilimumab has been administered as single and multiple doses, as single agent therapy, and in combination with vaccine, chemotherapy, or interleukin-2 (IL-2) to more than 650 patients to date. Although the majority of studies have focused on patients with metastatic melanoma, studies have included patients with prostate cancer, lymphoma, renal cell cancer, breast cancer, ovarian cancer, and human immunodeficiency virus (HIV).

Phase I trials of ipilimumab in patients with progressive, metastatic, hormone-refractory prostate cancer (HRPC), MDX-010-01 (n=14) or Stage III or IV malignant melanoma MDX-010-02 (n=17) have been completed. Five (36%) of the 14 patients treated on study MDX-010-01 experienced 1 or more AEs considered by the Investigator to be related to treatment with ipilimumab. The majority of AEs experienced were of Grade 1 (2 patients; 14%) or Grade 2 (2 patients; 14%) severity. The most common AEs reported included rash and pruritus (2 patients; 14%). Responses were observed in 2 patients (as determined by a greater than 50% decrease from baseline in prostate-specific antigen [PSA] levels).

Patients in study MDX-010-02 experienced AEs of primarily Grade 1 (4 patients; 24%) or Grade 2 (8 patients; 47%) severity. The most common AEs reported included rash (5 patients; 29%), fatigue (5 patients; 29%), arthralgia (5 patients; 29%), erythematous rash (4 patients; 24%), nausea (4 patients; 24%), and positive antinuclear factor (4 patients; 24%). One of the patients with a positive antinuclear factor also developed clinically insignificant retinal pigment changes.

The relationship of retinal pigment change to ipilimumab is unknown, as pigment changes have been previously described in melanoma. Two out of seventeen patients had an objective response, for an objective response rate of 12%. Additional mixed or stable disease responses were also seen in both MDX-010-01 and MDX-010-02 trials.

The relevant Phase I/II studies of ipilimumab therapy in metastatic melanoma are summarized in the Investigator Brochure. Safety, tolerability, and anti-tumor activity are being assessed in all studies, and the pharmacokinetic profile of ipilimumab is being assessed in protocols MDX-010-02, MDX-010-08, and MDX-010-15.

Additional Phase I and II studies are currently ongoing with ipilimumab alone and in combination with other treatment modalities for multiple indications, including prostate cancer, melanoma, renal cancer, breast cancer and HIV.

In general, single and multiple doses of ipilimumab administered at dosages ranging from 1 to 10 mg/kg/dose q3 or q4 weeks appear to be associated with few infusion toxicities, but immune-mediated toxicity has been observed more frequently. With the exception of these immune-mediated toxicities, termed Immune Related Adverse Events (IRAEs), the AE profile is similar to what would be expected in a patient population consistent with the eligibility criteria of this protocol.

Drug-related serious AEs have occurred in conjunction with the administration of melanoma peptide vaccines as well as in the absence of concomitant vaccination. One hundred eighty (28%) of the more than 650 patients first treated with ipilimumab have reported SAEs; 44% of these patients have experienced AEs considered (although not proven) to be immune-mediated in nature and a consequence of the intrinsic biological activity of ipilimumab. These AEs are an expected consequence of inhibiting CTLA-4 function. Immune-mediated events, termed Immune Breakthrough Events (IRAEs), are AEs associated with drug exposure and consistent with an immune-based mechanism of action. In terms of organ system involvement, these events have primarily involved the gastrointestinal (GI) tract (diarrhea and colitis) or the skin (rash and pruritus). Diarrhea due to treatment with ipilimumab ranges from mild to very severe and may become life-threatening. Most cases of diarrhea and colitis have resolved with symptomatic treatment or corticosteroid intervention without known sequelae. Upper GI tract involvement including ileitis, duodenitis, and esophagitis has been observed. Bowel wall biopsies have usually revealed a pleomorphic infiltrate, including many lymphocytes, consistent with colitis due to an immune-mediated process. Within all of the ipilimumab protocols, the incidence of

serious drug related diarrhea, colitis, or gastrointestinal hemorrhage has been 16%. One patient in the combination arm of study MDX-010-08 (ipilimumab at 3 mg/kg and dacarbazine) developed hematochezia and immune-mediated colitis. Another patient in the combination arm of study MDX-010-08 developed hepatic necrosis and shock as a complication attributed to dacarbazine and ipilimumab (see Investigator Brochure).

Skin toxicity has manifested as rash and pruritus; when biopsied, pleomorphic infiltrates have been noted in the skin. Some patients have developed vitiligo associated with ipilimumab administration.

Of the more than 650 patients treated to date on a range of doses and schedules, approximately 1 - 2% of patients have experienced hypopituitarism to date presumably due to immune-mediated hypophysitis. Corticosteroid treatment has resulted in resolution of clinical symptoms in patients with hypopituitarism.

Ocular inflammation, specifically Grade 2 or Grade 3 episcleritis or uveitis, has been reported in 6 patients; it has occurred in conjunction with GI symptoms in 4 of these patients.

In addition, primary adrenal insufficiency has been noted in 3 patients. One case each of immune-mediated meningitis and granulomatous tubulointerstitial nephritis has been associated with ipilimumab administration.

A total of 66 patients have been treated with the 3 mg/kg dose in combination with peptide vaccines in studies MDX-010-03, MDX-010-05, and MDX-010-16. Patients have tolerated the study therapy well in these studies, with the most common side effects being Grade 1 or 2: nausea, diarrhea, non specific abdominal pain, fatigue, pyrexia, arthralgias, rash and rigors. The overall incidence of related serious AEs was 18%. There was a death due to liver failure, respiratory failure, renal insufficiency and sepsis in a patient treated with ipilimumab 3 mg/kg and melanoma peptide vaccination (see Investigator Brochure). Thirteen patients have been treated in MDX-010-04, which uses the 3 mg/kg dose with melacine and cyclophosphamide. Therapy has been tolerated well, with Grade 1 or 2: nausea, vomiting, diarrhea, and fatigue being most common. The overall incidence of related SAEs was 15%.

Melanoma Ipilimumab Update

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. Please see the investigator brochure for additional details.

Ipilimumab has been administered to more than 1500 patients with different cancers in more than 20 clinical trials to date with a dose range between 0.1 mg/kg and 20 mg/kg. Most experience with ipilimumab exists at the 3 mg/kg and 10 mg/kg dose levels. Patients who received ipilimumab at 3mg/kg were treated in clinical trials conducted early in the development program and received either a single or multiple injections. Intra-patient dose escalation indicated that patients with no responses at 3 mg/kg dose levels may respond to 9 mg/kg. The currently ongoing clinical program investigating ipilimumab in metastatic melanoma utilizes the 10 mg/kg dose level with the expectation that 10 mg/kg will prove more beneficial than 3 mg/kg. The current melanoma program utilizes a schedule consisting of an induction (10 mg/kg of ipilimumab q3weeks for four doses) followed by a maintenance phase for patients with response or stable disease (10 mg/kg q3 months).

The adverse event (AE) profile of ipilimumab is relatively well characterized with drug-related AEs mostly being immune-related adverse events (IRAEs), which are considered to be associated with the mechanism of action of impilimumab. Most common IRAEs are colitis and diarrhea, rash, pruritis, deficiencies of endocrine organs (pituitary, adrenal or thyroid), hepatitis, or uveitis. Rare complications are bowel perforations (~1%) resulting from underlying severe colitis, which have required surgical intervention.

As of March 5, 2007, preliminary data on 406 patients from the ongoing melanoma program is available in the clinical database. 50% of patients in this data set have shown Immune-Related Adverse Events (IRAEs) with 2/3 being low-grade and 1/3 being high-grade. 32% of patients had skin IRAEs of rash or pruritus, 23% had GI IRAEs of colitis or diarrhea, 6% hepatobiliary and 2% endocrine IRAEs. As of January 31, 2007 data from the Serious Adverse Event (SAE) safety database demonstrates the overall SAE rate for melanoma patients receiving ipilimumab in BMS trials (N=510) was approximately 30%, while the rate of patients with drug-related SAEs was approximately 15%. The rate of patients with IRAEs considered SAEs was approximately 12% with 7.1% GI, 2.7% hepatic and 1.8% endocrine events.

Strict dose modification criteria for toxicity and management algorithms for diagnosing and treating IRAEs were utilized in these patients as they are planned for this trial. These algorithms have been instrumental in avoiding complications resulting from IRAEs such as bowel perforations and hepatic failure, of which there was only one case each in the above population.

Resolution of IRAEs was achieved in most patients using the above criteria. Some patients with endocrine IRAEs requiring hormone replacement therapies are still being followed and resolution cannot be assessed.

While many low-grade IRAEs respond well to symptomatic therapy, high-grade IRAEs require steroid therapy and, in rare steroid-refractory cases, the use of other immune suppressive therapies such as infliximab or mycofenolate mofetil. Management algorithms are established for diagnosing and treating IRAEs of diarrhea/colitis and hepatitis; a third algorithm for endocrinopathies is being developed.

Summary of Effects in Humans

Ipilimumab has been administered as single and multiple doses and in combination with chemotherapy, cytokines, and peptide vaccines. Data from a total of 1654 subjects with a variety of cancer types had been entered into the clinical database and are reported within the investigator brochure. Approximately 1500 subjects studied had advanced melanoma. In addition to melanoma, the tumor types studied include protate cancer, renal cell cancer, breast cancer, ovarian cancer, synovial sarcoma, pancreatic cancer, hematologic malignancies, and non-Hodgkin's lymphoma. Clinical studies are listed in the investigator's brochure Table 5A (melanoma studies), Tanle 5B (non-melanoma studies), and Table 5C (collaborative studies).

Please refer to the Investigator Brochure for additional information and current summaries of clinical investigations with Ipilimumab.

Details of Intestinal Perforations or Serious Bleeding

As of September 2005, 7 patients in total have experienced gastrointestinal perforation or bleeding and 5 underwent colectomy. Three of these patients had melanoma (representing 0.6% of all patients with melanoma enrolled in ipilimumab related protocols) while four patients had renal cell carcinoma (representing 7% of all patients with renal cell carcinoma enrolled in ipilimumab related protocols). There have been no reported gastrointestinal perforations or colectomies in patients with breast or prostate cancer. The overall incidence of gastrointestinal perforations and/or colectomies is < 2% of patients. The 7 patients with intestinal perforation or bleeding requiring colectomy are described in the Investigator Brochure.

With the exception of the uncommon (< 2%) cases requiring colectomy, these immune-mediated AEs have been readily manageable and reversible with supportive care or corticosteroid treatment.

Details of Drug-Related Deaths

As of September 2005, there have been 4 deaths possibly related to administration of ipilimumab. One patient died from GI perforation. Two patients died of multi-organ failure (in one case, concomitant use of DTIC was also suspected as causative agent). One death was related to possible cerebral vascular accident (CVA), pulmonary embolus and sepsis. Please refer to the Investigator Brochure for additional information.

Clinical Efficacy to Date

Interestingly, about 41% of the patients developing an immune-mediated adverse event in several studies have also experienced a clinical response (Table 1), including the patient with hypopituitarism, who demonstrated a durable complete response. These adverse events, potentially reflecting a loss of tolerance to some self antigens, or hyper response to bacterial antigens presented in the gut or skin and are therefore proposed to be mechanism related and may be directly linked to the clinical anti-tumor activity of ipilimumab.

Table 1 Association Between Response and Immune Breakthrough Events In Patients Receiving ipilimumab

	Patients with Serious IRAEs Response Rate (%)	Patients without Serious IRAEs Response Rate (%)	p-value (Fisher's exact test)
Monotherapy[a]	5/6 (83%)	6/35 (17%)	0.0032
IPILIMUMAB *plus* GP100 vaccine[b]	2/6 (33%)	1/31 (3%)	0.0624
IPILIMUMAB *plus* dacarbazine[a]	2/10 (20%)	3/25 (12%)	0.6103

[a] 3mg/kg Q 3 weeks (MDX-010-08)

[b] 3mg/kg Q 3 weeks or 3 mg/kg initial dose followed by 1 mg/kg Q 3 weeks (MDX-010-05)

Fisher's exact test was performed to examine the difference in the IRAE incidence rate between responders and non-responders. In the monotherapy study, a statistically significant association was observed between response and IRAEs ($p = 0.0032$).

As of September 2005, efficacy with the 3 mg/kg dose of ipilimumab has been observed in a number of settings following treatment as monotherapy and in combination with other agents. Specifically, 2/17 (12%) objective partial responses were observed in metastatic melanoma patients receiving single-dose, 3 mg/kg, ipilimumab in study MDX-010-02. Two of the PRs were detected early in the treatment course (after up to 2 doses of ipilimumab). The median duration of the partial responses was 4.5 months. Multi-dose application of the same dose resulted in 2/37 objective partial responses (5%) but with longer observed durability of response (16+ and 18+ months). In combination with IL-2, 3 mg/kg every 3 weeks ipilimumab in study MDX-010-13, resulted in 9/36 (25%) objective responses with 3 (8%) achieving complete responses. In combination with a melanoma-specific vaccine, gp100, the observed response rate was 7/56 (13%) with 2 (4%) CRs and a median durability of response of 35+ months.

In Study MDX-010-015, 24 patients were enrolled to receive 10 mg/kg every 3 weeks for four doses. As of September 2005, the first (Week 12) tumor response results were available on 12 patients. One patient (8%) had an objective response with 90% overall reduction in the sum of the longest diameters by Response Evaluable Criteria in Solid Tumors (RECIST) criteria. Three patients (25%) had evidence of tumor shrinkage that was short of a partial response (PR) by RECIST criteria (20%, 20% and 29% reduction in the sum of the longest diameters, respectively). One patient (8%) had stable disease (SD) and 7 (58%) had progressed. Further Follow-Up is pending on all non-progressing patients.

Study MDX-010-08 explored the safety and efficacy of ipilimumab (3 mg/kg) with dacarbazine. Patients were randomized to receive ipilimumab at 3 mg/kg monthly x 4 (Arm A; n=37) or ipilimumab in combination with dacarbazine 250 mg/m^2 for 5 days monthly x 4 (Arm B; n=35). Clinical response was measured by RECIST criteria at Week 12 and patients were followed every 12 weeks until disease progression. In Arm A there were 2 PRs (ORR 5%) and 4 SD. In Arm B there were 2 CRs and 4 PRs (ORR 17%) as well as 4 SDs. Long-term durable objective responses and disease stabilization were observed in both monotherapy and combination arms of the study. In Arm A the 2 PRs are continuing at 11.9+ and 14+ months, and 1 patient with stable disease is ongoing at 18.2+ months. In Arm B the 2 CRs are continuing at 12.6+ and 16.3+ months, and 1 PR is ongoing at 16.7+ months. The median progression-free survival in Arm A is

82 days and 99 days in Arm B. The data from both treatment arms also showed an increase in overall survival (11.2 months in the monotherapy arm and 14.8 months in the combination arm) when compared to historical data of dacarbazine alone (ranging from 4.5 to 6.4 months).

Therefore, ipilimumab alone or in combination with dacarbazine, induced durable (i.e., > 1 year) objective clinical responses in previously untreated patients with metastatic melanoma. The best overall response rate (BORR) observed in patients treated with the combination of dacarbazine and ipilimumab appears higher than reported with dacarbazine alone (6%). Furthermore, it should be noted that the overall survival rate (OS) in the dacarbazine/ipilimumab combination arm was observed to be 30% higher than the arm that received ipilimumab alone, suggesting an increased clinical benefit when dacarbazine is added to the anti-CTLA-4 antibody.

Full information on expected toxicities can be found in the Investigator's Brochure, version 8.0 (12-Oct-05).

Method for Assessment of Immune Related Clinical Responses with Ipilimumab

It is becoming increasingly clearer that the assessment of clinical activity with immune mediated therapies such as ipilimumab requires new definitions of meaningful endpoints. Extensive clinical activity with ipilimumab both at the Dana-Farber/Harvard Cancer Center and with recently completed multi-center international trials has revealed that ipilimumab induces in many patients during the first 12 weeks of therapy significant immune infiltrates and edema that cannot be easily appreciated by standard radiographic procedures. The anti-tumor effects from ipilimumab also require time to develop. It is believed that within the first 12 weeks of therapy, the immune system recognizes and destroys cancer cells that possess the primary antigen repertoire. Also, during this time, "Immuno-sculpting" results in a new antigen repertoire which appears radiographically as metastatic sites. Inflammation, therefore, may be present in responding but not new lesions at week 12. With further radiographic and clinical assessments over time and continued ipilimumab treatment, the new lesions' antigen repertoire is recognized and radiographic response is noted. Biopsies of these regressing lesions now demonstrate inflammation.

Overall Risk/Benefit Assessment for Ipilimumab

Ipilimumab has demonstrated durable tumor regressions both as monotherapy at 3 mg/kg every 3 weeks, in patients escalated to 9 mg/kg q3 weeks, in combination with dacarbazine, in

combination with IL-2 and in combination with gp100 vaccine. Ipilimumab administered as single agent or in combination with vaccine or chemotherapy has generally been well tolerated in the majority of patients. As would be expected with the addition of chemotherapy, the incidence of related serious AEs increased to 14.3% for the combination of ipilimumab dosed at 3 mg/kg and dacarbazine, vs. 8.5% for ipilimumab 3 mg/kg monotherapy.

To date, 24 patients in the MDX-010-015 study have been treated with a single 10 mg/kg dose and have generally tolerated this regimen.

Significant drug-related immune-mediated phenomena have been observed in some patients who receive multiple doses of ipilimumab, most commonly including rash and pruritus. Some patients with melanoma have developed vitiligo. Colitis, manifesting as diarrhea (including Grade 3 diarrhea and/or bloody diarrhea requiring hospitalization and uncommonly [< 2%] requiring colectomy) has been the most clinically significant drug-related AE. Immune-mediated AEs, or so-called IRAEs, appear to have an association with anti-tumor activity.

Immune-Related Adverse Events (IRAEs)

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

Approximately 60% of subjects developed any grade IRAEs which predominately involved the GI tract, endocrine glands, liver, or skin. Based on data from the safety database, the number of subjects with serious IRAEs was approximately 13% (214/1654), including 8% for serious GI IRAEs (diarrhea and/or colitis), 2% of serious endocrinopathy (primarily hypophysitis/hypopituitarism) and <1% of serious skin IRAEs. Bowel perforation was reported in approximately 1% of subjects. With few exceptions these IRAEs were clinically manageable

and reversible with supportive care or corticosteroids. In responding patients, addition of corticosteroids does not appear to have a temporal relationship to change in objective tumor response.

Additionally, as of February 2006, there has been observation from a National Cancer Institute (NCI) study of bowel wall perforation in some patients who were administered a high-dose IL-2 following treatment with ipilimumab. Of the 22 patients administered high-dose IL-2, three patients experienced bowel wall perforations. This is a higher rate than would be expected with high-dose IL-2 treatment alone. All three patients had metastatic melanoma and had previously received their last dose of ipilimumab > 77 days before the first dose of IL-2. Two of the patients had clinically significant ipilimumab-related diarrhea or colitis and the symptoms had completely resolved prior to IL-2 administration. One patient did not experience ipilimumab-related diarrhea. It is unknown whether this observation represents a true association or is mechanistically unrelated to prior ipilimumab exposure.

Drug Related Deaths

Based on reports from the safety data base as of 31-Mar-2007, there have been reports of death (approximately 1% {20/2000}), deemed by the investigator as possibly related to the administration of study drug. The most common cause of drug related deaths was gastrointestinal (GI) perforation. Other causes included multiorgan failure, sepsis, hypotension, acidosis and adult respiratory distress syndrome. For details on all drug related deaths please refer to the most recent version of IB.

Safety of 10 mg/kg Ipilimumab (MDX-010) Multiple Doses

Data on the 10 mg/kg dose level primarily comes from 6 studies (5 in subjects with melanoma and 1 in subjects with prostate cancer) in which all patients enrolled received the 10 mg/kg dose level of ipilimumab. Additional ongoing studies are evaluating the safety data in which blinded study therapy includes 10 mg/kg ipilimumab. Based on the limited experience with 10 mg/kg multiple doses of ipilimumab, it appears the overall safety profile for the 10 mg/kg ipilimumab was consistent with that of the 3 mg/kg ipilimumab. However, there is a potential that some drug-related SAEs are IRAEs may occur more frequently with the 10 mg/kg ipilimumab, e.g. GI, hepatic and endocrine systems. Please refer to the most updated IB, including addenda for details.

Bevacizumab is a well studied drug with extensive experience in patients with solid tumors. For patients with metastatic melanoma, there is little convincing evidence that any standard systemic therapy prolongs life. New treatment regimens, therefore, are needed for this patient population.

Therefore, the overall risk and benefit for patients entering this protocol are considered acceptable to allow accrual with Informed Consent being obtained from all patients.

1.4 Dana-Farber/Harvard Cancer Center Experience with Ipilimumab

Blocking the attenuation of T cell activation by cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) has proven anti-tumor biologic activity in patients, but with significant reports of autoimmune reactivity. In efforts to maximize the anti-tumor effects while limiting the likelihood of autoimmunity, we undertook a phase I study administering a CTLA-4 blocking antibody (MDX-010; ipilimumab) to metastatic melanoma and ovarian cancer patients who had previously received vaccination with irradiated, autologous tumor cells engineered to secrete GM-CSF (GVAX)(Hodi et al. PNAS, 2003; 100:4712). Patients received a 3 mg/kg infusion of MDX-010 every 2-3 months. We treated 14 stage IV melanoma patients and 10 patients with stage IV ovarian cancer immunized with GVAX. Reticular, erythematous rashes reflecting melanocyte auto-reactivity in 13/14 and grade 1-2 constitutional symptoms in 4/14 melanoma patients were observed. Auto-antibodies were detected in 10/14 melanoma patients, but without clinical evidence of autoimmunity. MDX-010 stimulated extensive tumor destruction with lymphocyte and granulocyte infiltrates in 4 of 5 melanoma patients who received prior GVAX when sites or pre-existing disease were biopsied following treatment. Seven of 11 have remained with radiographic stable disease and one patient with a radiographic partial response that was delayed and who has received a total of 8 doses. In treated ovarian cancer patients, 5/10 developed a lupus-like rash and 2/10 developed inflammatory gastritis/colitis. Five of 10 experienced a reduction or stabilization of CA-125 levels with one patient with normal CA-125 level having extensive hemorrhagic tumor necrosis revealed by biopsy of pre-existing disease following treatment. One ovarian patient has received more than six doses and continues to experience dramatic reductions in CA-125 with tumor regression.

Our own experience with ipilimumab involves its administration to patients following a therapeutic vaccine. In patients who we have biopsied pre-existing sites of disease following treatment, we have witnessed pathologically the consistent presence of an immune mediated

vasculopathy to the vasculature feeding the tumor deposit associated with extensive tumor necrosis. Please see accompanying figures (Figures 2 and 3).

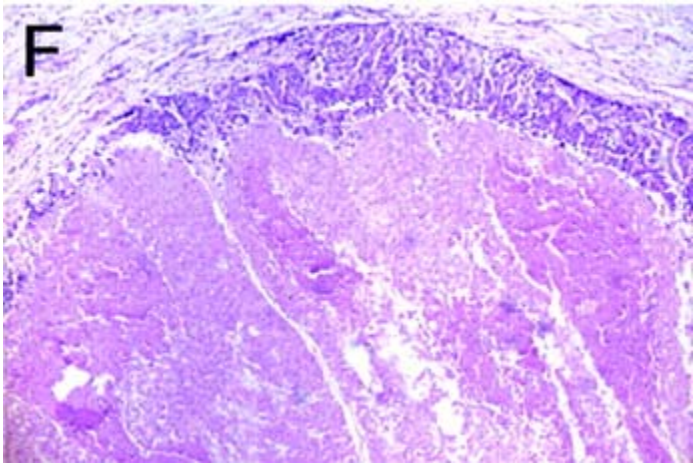


Figure 2: Melanoma deposit post-ipilimumab demonstrating extensive hemorrhagic tumor necrosis with rim of viable tumor heavily infiltrated with granulocytes and lymphocytes.

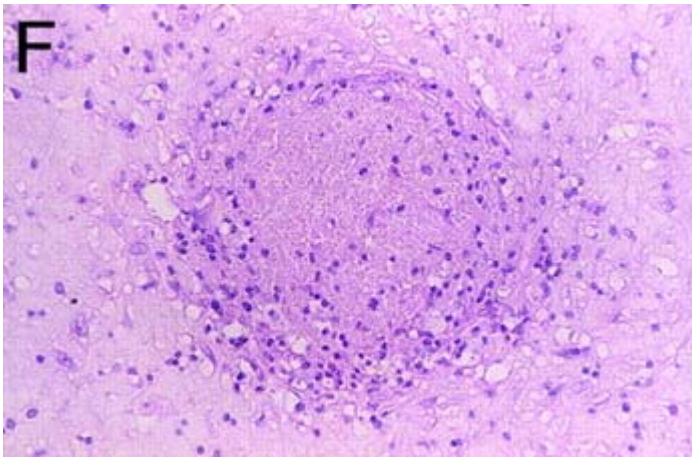


Figure 2: Melanoma tumor deposit post-ipilimumab with severe tumor vasculopathy accompanied by perivascular and intramural lymphoid infiltrates associated with luminal thrombosis. (Magnification: ×125)

We are currently performing laboratory investigations to further define the targets of response to ipilimumab involved in tumor angiogenesis. These assays for biologically active molecules involved in tumor related angiogenesis and the means to assess the immune responses to these molecules are currently being established in the laboratory and will be available for correlative studies related to this trial. Through the Immune Assessment Core of the Cancer Vaccine Center at Dana-Farber, cellular and humoral immune responses to established melanoma antigens are

being performed. Based upon recent laboratory findings, we are also continuing to investigate the effects of VEGF and other angiogenic molecules on regulatory T cell function.

1.5 Study Rationale

The observation of the vascular effects of ipilimumab on tumor deposits further supports the critical importance of angiogenesis to tumor growth. The clinical efficacy of targeting VEGF and its effect on pathologic angiogenesis has been extensively studied with the use of bevacizumab. There is also increasing evidence for the effects of VEGF on immune regulatory cell function. Given the profound effects on tumor vasculature witnessed in melanoma patients being treated with ipilimumab and the known effects of bevacizumab, we propose a phase I study testing the combination of these two drugs in patients with metastatic melanoma.

Bevacizumab is a FDA approved drug with extensive clinical experience. The dose ranges of ipilimumab have been extensively tested in patients as a single agent.

2.0 OBJECTIVES

2.1 Primary

To determine the safety, tolerability and maximum tolerated dosing for the combination of bevacizumab plus ipilimumab in patients with unresectable stage III or stage IV melanoma

2.2 Secondary

To determine the best overall response rate by standard solid tumor response criteria, disease control rate, time to tumor progression, and duration of response for the combination of bevacizumab plus ipilimumab in patients with unresectable stage III or stage IV melanoma.

To perform correlative studies investigating the effects of this combination therapy on anti-tumor immunity and tumor vasculature.

To gain additional information about the effect of the combination of ipilimumab and bevacizumab upon secondary outcomes and correlative studies in two cohorts treated with ipilimumab 3 mg/kg and bevacizumab at 7.5 mg/kg or 15 mg/kg.

3.0 STUDY DESIGN

3.1 Description of the Study

After informed consent is obtained, patients will be assessed for eligibility criteria. Upon meeting criteria, eligible patients will be entered to receive bevacizumab and ipilimumab treatment and disease assessments. Disease response and patient tolerability to this combination will determine whether, and in what capacity, patients will be allowed to continue on study.

Patients who do not meet eligibility criteria will not enter the treatment phase and additional patients will be enrolled in their place.

Open label, phase I trial testing the combination of bevacizumab and ipilimumab in patients with metastatic melanoma.

We will begin with the standard dose and schedule of Ipilimumab shown to be effective in patients with metastatic melanoma. In the first cohort, we will combine with the lowest dose of bevacizumab shown to have biologic activity. If safe, we will increase the bevacizumab to the full standard dose (cohort 2). If cohort one has unacceptable toxicities, Ipilimumab dose will be decreased (cohort 3) (following discussion and written approval by Bristol-Myers Squibb). If cohort 3 has an acceptable safety profile, cohort 4 will test the decreased dose of Ipilimumab with full standard dose of bevacizumab.

Cohort 1: Ipilimumab 10 mg/kg IV every 3 weeks x 4 doses(induction), then every 3 months (maintenance); Bevacizumab 7.5 mg/kg IV every 3 weeks (continuous)

Cohort 2: Ipilimumab 10 mg/kg IV every 3 weeks x 4 doses (induction), then every 3 months (maintenance); Bevacizumab 15 mg/kg IV every 3 weeks (continuous)

Cohort 3: Ipilimumab 3 mg/kg IV every 3 weeks x 4 doses (induction), then every 3 months (maintenance); Bevacizumab 7.5 mg/kg IV every 3 weeks (continuous)

Cohort 4: Ipilimumab 3 mg/kg IV every 3 weeks x 4 doses (induction), then every 3 months (maintenance); Bevacizumab 15 mg/kg IV every 3 weeks (continuous)

Five patients may be entered for each study cohort. If three or more patients in Cohort 1 experience dose limiting toxicity (DLT) during the first 12 weeks, then that cohort will be determined to have unacceptable toxicity; otherwise, escalation to Cohort 2 will be made. If

Cohort 1 is found to have unacceptable toxicity, then patients may be enrolled in Cohort 3 following discussion between the Principal Investigator and Bristol-Myers-Squibb (BMS) and written approval from a BMS representative is obtained to enroll in Cohort 3. If toxicities in Cohort 3 are acceptable, patients may enroll in Cohort 4. If three or more patients in Cohort 3 experience DLT, then the study will be halted until further discussion with BMS. There will be no escalation from Cohort 2 to Cohort 3. An additional 12 patients will be treated at the MTD cohort to increase the likelihood of detecting serious toxicities, gain preliminary experience with biologic activity, and to complete biologic correlative endpoints.

Before escalation to the next dose level, three patients in a cohort must complete the 12 weeks of induction treatment without dose limiting toxicities.

Patients may be replaced if they experience rapid progression of disease within the first four weeks of registration that requires alternative treatment and/or palliation. Patients may not be replaced for any other reason. Patients in a cohort exhibiting DLT will not be replaced. Up to two patients may be replaced in any cohort due to rapid disease progression without exhibiting DLT. There will be no dose escalation within a cohort.

As of June 2010, patients have safely been treated on cohorts 1 and 2. The MTD was determined to be ipilimumab 10 mg/kg and bevacizumab 15 mg/kg. Data from a previously conducted phase III trial (Hodi et al.NEJM 2010) have demonstrated that ipilimumab at 3 mg/kg offers a survival advantage for patients with metastatic melanoma. In order to gain additional experience with this drug combination utilizing ipilimumab at 3mg/kg, cohorts 3 and 4 will be opened to enroll an additional 12 patients in each cohort. The first 12 additional patients will be enrolled in cohort 3 at ipilimumab 3 mg/kg IV every 3 weeks x 4 doses (induction), then every 3 months (maintenance); bevacizumab 7.5 mg/kg IV every 3 weeks (continuous). Following accrual to this cohort, an additional 12 patients will be accrued to cohort 4 at ipilimumab 3 mg/kg IV every 3 weeks x 4 doses (induction), then every 3 months (maintenance); bevacizumab 15 mg/kg IV every 3 weeks (continuous). The data from these cohorts will be assessed for secondary and correlative outcomes. Since the combination of ipilimumab and bevacizumab at the higher, MTD dosage has been well-tolerated, we do not anticipate a greater incidence of adverse events with the dose combinations of cohorts 3 and 4, although safety and tolerability will be carefully monitored and reported. Our primary clinical interest in these latter cohorts will be their effect upon secondary and correlative measures.

4.0 STUDY SUBJECTS

4.1 Inclusion Criteria

Patients must have:

Eligibility

1. Measurable unresectable Stage III or Stage IV melanoma
2. ECOG PS 0,1
3. ≥4 weeks since treatment (chemo-, radiation, hormone, immuno-, etc., therapy)
4. Patients must have recovered from any acute toxicity associated with prior therapy
5. Life expectancy ≥12 weeks
6. Willing and able to give written informed consent
7. Due to the unknown effects of this treatment on the fetus or nursing infant, pregnant or nursing women should not be included. Women should be either: post-menopausal for at least 1 year; surgically incapable of bearing children; or utilizing an intrauterine device, and/or spermicide and barrier, for contraception. During the study, use of oral contraception alone is not acceptable. Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the study and for up to 8 weeks after the study in such a manner that the risk of pregnancy is minimized. Even women who are using oral, implanted or injectable contraceptive hormones or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy or practicing abstinence or where partner is sterile (e.g., vasectomy), should be considered to be of child bearing potential.

   Women of childbearing potential must have a negative serum β-HCG pregnancy test conducted during screening, and a negative urinary β-HCG pregnancy test conducted within 24 hours prior to treatment.
8. Due to the unknown effects on the fetus, men should not father children during treatment
9. Age ≥ 18 years old.
10. WBC ≥ 2,500 cells/ μl
11. ANC ≥ 1000 cells/μl
12. Lymphocytes ≥ 500 cells/ μl
13. Serum creatinine ≤ 2 mg/dL
14. Platelets ≥ 100,000 cells/ μl
15. AST ≤ 2 x ULN
16. ALT ≤ 2 x ULN
17. Total Bilirubin ≤ 2 x ULN
18. Negative screening tests for HIV, active Hepatitis B, and Hepatitis C
19. Patients who received prior therapy with anthracylines should have a baseline MUGA or echo with a normal ejection fraction

4.2 Exclusion Criteria

1. CNS metastases
2. Pregnant or nursing women
3. Prior therapy with bevacizumab or ipilimumab
4. Active infection
5. Autoimmune disease: Patients with a history of inflammatory bowel disease are excluded from this study as are patients with a history of symptomatic autoimmune disease (e.g., rheumatoid arthritis, systemic progressive sclerosis (scleroderma), Systemic Lupus Erythematosus, autoimmune vasculitis (e.g., Wegener's Granulomatosis)
6. Any other malignancy from 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
7. Any underlying medical condition which, in the principal investigator's opinion, will make the administration of study drug hazardous or obscure the interpretation of adverse events
8. Any concurrent medical condition requiring the use of systemic steroids. (Use of inhaled or topical steroids is acceptable.)
9. Inability to comply with study and/or follow-up procedures
10. Inadequately controlled hypertension (defined as systolic blood pressure >150 and/or diastolic blood pressure > 100 mmHg on antihypertensive medications)
11. Any prior history of hypertensive crisis or hypertensive encephalopathy
12. New York Heart Association (NYHA) Grade II or greater congestive heart failure
13. History of myocardial infarction or unstable angina within 6 months prior to study enrollment
14. History of stroke or transient ischemic attack within 6 months prior to study enrollment
15. Significant known vascular disease (e.g., aortic aneurysm, aortic dissection)
16. Symptomatic peripheral vascular disease
17. Evidence of bleeding diathesis or coagulopathy
18. Major surgical procedure or significant traumatic injury within 28 days prior to study enrollment
19. Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to study enrollment
20. History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to study enrollment
21. Serious, non-healing wound, ulcer, or bone fracture
22. Proteinuria at screening as demonstrated by either
    -Urine protein:creatinine (UPC) ratio $\geq$ 1.0 at screening OR
    -Urine dipstick for proteinuria $\geq$ 2+ (patients discovered to have $\geq$2+ proteinuria on dipstick urinalysis at baseline should undergo a 24 hour urine collection and must demonstrate $\leq$ 1g of protein in 24 hours to be eligible)
23. Known hypersensitivity to any component of bevacizumab

24. History of hemoptysis (bright red blood of 1/2 teaspoon or more per episode) within 3 months prior to study enrollment
25. Current, ongoing treatment with full-dose warfarin or its equivalent (i.e., unfractionated and/or low molecular weight heparin). Subjects should have not taken full-dose warfarin or equivalent for at least 2 weeks prior to study entry
26. Current or recent (within 10 days of enrollment) use of aspirin (>325 mg/day) or chronic use of other NSAIDs
27. Medications that inhibit platelet function (e.g., dipryidamolde, epoprostenol, epitfibatide, clopidogrel, cilostazol, abciximab, ticlopidine, and ibuprofen and related compounds) also be excluded unless subject has been off treatment for at least 2 weeks prior to study enrollment.
28. Known involvement of melanoma within the gastrointestinal tract
29. Ulcerated skin lesions

4.3 SUBJECT ENROLLMENT

Ethics

This study will be conducted in accordance with the ethical principles that have their origin in the current Declaration of Helsinki and will be consistent with International Conference on Harmonization Good Clinical Practice (ICH GCP) and applicable regulatory requirements.

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

Freely given written informed consent must be obtained from every subject prior to clinical trial participation, including informed consent for any screening procedures conducted to establish subject eligibility for the trial.

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

Study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s).

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

Patients who meet eligibility requirements and who give written informed consent must first be registered with the Quality Assurance Office for Clinical Trials (QACT) at DFCI, prior to the beginning of the treatment. The phone number of this office is 632-3761 and the fax number is 632-2295.

Subjects may be removed from the study in the following situations:

1. Withdrawal of consent
2. Non-compliance

5.0 Treatment Plan

We will begin with the standard dose and schedule of Ipilimumab shown to be effective in patients with metastatic melanoma. In the first cohort, we will combine with the lowest dose of bevacizumab shown to have biologic activity. If safe, we will increase the bevacizumab to the full standard dose (cohort 2). If cohort one has unacceptable toxicities, Ipilimumab dose will be decreased (cohort 3) (following discussion and written approval by Bristol-Myers Squibb). If cohort 3 has an acceptable safety profile, cohort 4 will test the decreased dose of Ipilimumab with full standard dose of bevacizumab.

Cohort 1: Ipilimumab 10 mg/kg IV every 3 weeks x 4 doses (induction), then every 3 months (maintenance); Bevacizumab 7.5 mg/kg IV every 3 weeks (continuous)

Cohort 2: Ipilimumab 10 mg/kg IV every 3 weeks x 4 doses (induction), then every 3 months (maintenance); Bevacizumab 15 mg/kg IV every 3 weeks (continuous)

Cohort 3: Ipilimumab 3 mg/kg IV every 3 weeks x 4 doses (induction), then every 3 months (maintenance); Bevacizumab 7.5 mg/kg IV every 3 weeks (continuous)

Cohort 4: Ipilimumab 3 mg/kg IV every 3 weeks x 4 doses (induction), then every 3 months (maintenance); Bevacizumab 15 mg/kg IV every 3 weeks (continuous)

Five patients may be entered for each study cohort. If three or more patients in Cohort 1 experience dose limiting toxicity (DLT) during the first 12 weeks, then that cohort will be determined to have unacceptable toxicity; otherwise, escalation to Cohort 2 will be made. If Cohort 1 is found to have unacceptable toxicity, then patients may be enrolled in Cohort 3 following discussion between the Principal Investigator and Bristol-Myers-Squibb (BMS) and written approval from a BMS representative is obtained to enroll in Cohort 3. If toxicities in

Cohort 3 are acceptable, patients may enroll in Cohort 4. If three or more patients in Cohort 3 experience DLT, then the study will be halted until further discussion with BMS. There will be no escalation from Cohort 2 to Cohort 3. An additional 12 patients will be treated at the MTD cohort to increase the likelihood of detecting serious toxicities, gain preliminary experience with biologic activity, and to complete biologic correlative endpoints.

Before escalation to the next dose level, three patients in a cohort must complete the 12 weeks of induction treatment without dose limiting toxicities.

Patients may be replaced if they experience rapid progression of disease within the first four weeks of registration that requires alternative treatment and/or palliation. Patients may not be replaced for any other reason. Patients in a cohort exhibiting DLT will not be replaced. Up to two patients may be replaced in any cohort due to rapid disease progression without exhibiting DLT. There will be no dose escalation within a cohort. Each patient will receive ipilimumab and bevacizumab according to the cohort assigned.

As of June 2010, patients have safely been treated on cohorts 1 and 2, with an MTD established at ipilimumab 10 mg/kg and bevacizumab 15 mg/kg. However, data from a previously conducted phase III trial have demonstrated that ipilimumab at 3 mg/kg offers a survival advantage for patients with metastatic melanoma. In order to gain additional experience with this drug combination utilizing ipilimumab at 3mg/kg, cohorts 3 and 4 will be opened to enroll an additional 12 patients in each cohort. The first 12 additional patients will be enrolled in cohort 3 at Ipilimumab 3 mg/kg IV every 3 weeks x 4 doses (induction), then every 3 months (maintenance); Bevacizumab 7.5 mg/kg IV every 3 weeks (continuous). Following accrual to this cohort, an additional 12 patients will be accrued to cohort 4 at Ipilimumab 3 mg/kg IV every 3 weeks x 4 doses (induction), then every 3 months (maintenance); Bevacizumab 15 mg/kg IV every 3 weeks (continuous).

Patients will receive ipilimumab first followed by bevacizumab. There is no planned delay between the ipilimumab and bevacizumab administration. If it is found that pre-medication is necessary prior to bevacizumab administration, then a delay is allowed.

5.1 Ipilimumab:

The dose of Ipilimumab will be infused over 90 minutes.

Subjects will be dosed using height and weight obtained on day of infusion. Each dose will be recalculated prior to each infusion.

Dose Calculations for Iplilimumab

Total dose for ipilimumab should be calculated as follows:

Subject body weight in kg x (study dose) = total dose, mg

Total infusion volume should be calculated as follows:

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

If the patient weighs more than 125.0 kg, the BMS protocol manager needs to be contacted to discuss the total infusion volume, infusion rate, and infusion duration.

Rate of infusion should be calculated as follows:

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

5.2 Bevacizumab:

Each patient will receive Bevacizumab IV every three weeks according to the cohort assigned; see section 3.1

Bevacizumab will be diluted in 0.9% Sodium Chloride Injection, USP, to a total volume of 100 mL. Administration will be as a IV infusion. Anaphylaxis precautions should be observed during study drug administration.

Subjects will be dosed using height and weight obtained on day of infusion. Each dose will be recalculated prior to each infusion. The initial dose will be delivered over 90±15 minutes. If the first infusion is tolerated without infusion-associated adverse events (fever and/or chills), the second infusion may be delivered over 60±10 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over 30±10 minutes.

If a subject experiences an infusion–associated adverse event, he or she may be pre-medicated for the next study drug infusion; however, the infusion time may not be decreased for the

subsequent infusion. If the next infusion is well tolerated with pre-medication, the subsequent infusion time may then be decreased by 30±10 minutes as long as the subject continues to be pre-medicated. If a subject experiences an infusion-associated adverse event with the 60-minute infusion, all subsequent doses should be given over 90±15 minutes. Similarly, if a subject experiences an infusion-associated adverse event with the 30-minute infusion, all subsequent doses should be given over 60±10 minutes.

5.3 CONCOMITANT MEDICATIONS

Low-dose aspirin (≤ 325 mg/d) may be continued in subjects at higher risk for arterial thromboembolic disease. Subjects developing signs of arterial ischemia or bleeding on study should be evaluated for possible bevacizumab discontinuation per Section 6.1, Table 2, Bevacizumab Dose Management Due To Adverse Events.

5.4 Continuation of Treatment

Patients will be staged every 12 weeks. Patients may continue treatment if there is evidence for stable or responsive disease by Immune Related Response Criteria. Experience with ipilimumab has proven that target lesions following treatment that enlarge radiographically may have evidence for tumor destruction and inflammation on histologic examination. Many months of treatment may be necessary until a response as assessed by traditional RECIST criteria are met, yet these patients are likely receiving benefit from such treatment. As a result, patients with immune related partial response, immune related stable disease, immune related mixed response or patients with up to 40% increase in the sum of the longest diameter with no more than two new target lesions may continue with treatment. Evaluations by standard response criteria will still be recorded for these patients. Maintenance with the combination should be at the induction dose for each patient.

5.5 Definition of DLT

National Cancer Institute's Common Toxicity Criteria for Adverse Events version 3.0 (CTCAE v3) will be used for all toxicity grading. DLT will be defined as any ≥ grade 3 toxicity not expected, a toxicity of grade 3 or higher, outlined in Dose Modification and Toxicity Management section of this protocol, that is not effectively managed with local or systemic immunosuppression within 7 days, eye pain of grade 2 or higher or uveitis of any grade, any

grade 4 immunological toxicity that is related to ipilimumab, or two delays of treatment (not due to scheduling non-compliance) each lasting more than 10 days within 4 cycles of drug.

DLT will include any expected toxicity of Grade 3 or higher, believed to be "possibly", probably" or "certainly" related to ipilimumab_and/or bevacizumab treatment outlined in the Dose Modification and Toxicity Management section of this protocol, that is not effectively managed according to the rules of the Dose Modification and Toxicity Management section.

6.0 Dose Modification and Toxicity Management

6.1 Bevacizumab Dose Modification and Toxicity Management

There are no reductions in the bevacizumab dose within a cohort. If adverse events occur that require holding bevacizumab, the dose will remain the same once treatment resumes.

Any toxicities associated or possibly associated with bevacizumab treatment should be managed according to standard medical practice. Bevacizumab has a terminal half-life of 2 to 3 weeks; therefore, its discontinuation results in slow elimination over several months. There is no available antidote for bevacizumab.

Subjects should be assessed clinically for toxicity prior to, during, and after each infusion. If unmanageable toxicity occurs because of bevacizumab at any time during the study, treatment with bevacizumab should be discontinued.

Infusion Reaction: Infusion of bevacizumab should be interrupted for subjects who develop dyspnea or clinically significant hypotension. Subjects who experience a NCI CTCAE v. 3.0 Grade 3 or 4 allergic reaction / hypersensitivity, adult respiratory distress syndrome, or bronchospasm (regardless of grade) will be discontinued from bevacizumab treatment.

The infusion should be slowed to 50% or less or interrupted for subjects who experience any infusion-associated symptoms not specified above. When the subject's symptoms have completely resolved, the infusion may be continued at no more than 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes if well tolerated. Infusions may be restarted at the full rate during the next cycle.

Adverse events requiring delays or permanent discontinuation of bevacizumab are listed in Table 2.

Regardless of the reason for holding study drug treatment, the maximum allowable length of treatment interruption is 2 months. A patient will be classified as having a DLT if there are two delays of treatment (not due to scheduling non-compliance) each lasting more than 10 days within four cycles of drug.

Table2: Bevacizumab Dose Management Due to Adverse Events

Event	Action to be Taken
Hypertension	
No dose modifications for grade 1/2 events	
Grade 3	If not controlled to less than 150/100 mmHg with medication, discontinue bevacizumab and patient is off study.
Grade 4 (including RPLS (confirmed by MRI) or hypertensive encephalopathy)	Discontinue bevacizumab and patient is off study.
Hemorrhage	
No dose modifications for grade 1/2 nonpulmonary and non-CNS events	
Grade ≥ 2 pulmonary or CNS hemorrhage	Discontinue bevacizumab and patient is off study.
Grade 3 nonpulmonary and non-CNS hemorrhage	Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other subjects will have study treatment held until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence. Subjects who experience a repeat Grade 3 hemorrhagic event will be discontinued from receiving bevacizumab.
Grade 4	Discontinue bevacizumab and patient is off study.
Venous Thrombosis	
No dose modifications for grade 1/2 events	

Grade 3/ Asymptomatic Grade 4	Hold study drug treatment. If the planned duration of full-dose anticoagulation is <2 weeks, study drug should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is >2 weeks, study drug may be resumed during the period of full-dose anticoagulation if all of the following criteria are met: • The subject must have an in-range INR (usually between 2 and 3) on a stable dose of warfarin (or other anticoagulant) prior to restarting study drug treatment. • The subject must not have had a Grade 3 or 4 hemorrhagic event while on anticoagulation. • The subject must not have had evidence of tumor involving major blood vessels on any prior CT scan.
Symptomatic Grade 4	Discontinue bevacizumab and patient is off study.

Arterial Thromboembolic event	
(Angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, and any other arterial thromboembolic event)	
Any grade	Discontinue bevacizumab and patient is off study.
Congestive Heart Failure (Left ventricular systolic dysfunction)	
No dose modifications for grade 1/2 events	
Grade 3	Discontinue bevacizumab and patient is off study
Grade 4	Discontinue bevacizumab and patient is off study.
Proteinuria	
No dose modifications for grade 1/2 events	
Grade 3 (UPC> 3.5, urine collection > 3.5 g/24 hr, or dipstick 4+)	Hold bevacizumab treatment until ≤ Grade 2, as determined by either UPC ratio ≤ 3.5 or 24 hr collection ≤ 3.5 g
Grade 4 (nephrotic syndrome)	Discontinue bevacizumab and patient is off study
GI Perforation	Discontinue bevacizumab and patient is off study.
Bowel Obstruction	
Grade 1	Continue patient on study for partial obstruction NOT requiring medical intervention.
Grade 2	Hold bevacizumab for partial obstruction requiring medical intervention. Patient may restart upon complete resolution.
Grade 3/4	Hold bevacizumab for complete obstruction. If surgery is necessary, patient may restart bevacizumab after full recovery from surgery, and at investigator's discretion, as long as the obstruction was related to an underlying tumor
Wound dehiscence requiring medical or surgical therapy	Discontinue bevacizumab and patient is off study.
Other Unspecified Bevacizumab-Related Adverse Events	
Grade 3	Hold bevacizumab until recovery to ≤ Grade 1
Grade 4	Discontinue bevacizumab and patient is off study.

Discontinuation of therapy:

Subjects who meet the following criteria should be discontinued from study treatment:

- Grade 4 hypertension or reversible posterior leukoencephalopathy syndrome (RPLS) or grade 3 hypertension refractory to medication
- Nephrotic syndrome
- Grade ≥ 2 pulmonary or CNS hemorrhage; any Grade 4 hemorrhage or repeat Grade 3 hemorrhage
- Grade 3 or greater hemorrhage while undergoing full dose anticoagulation
- Symptomatic Grade 4 venous thromboembolic event (any venous thromboembolic event requiring full dose warfarin or equivalent (i.e., unfractionated or low molecular weight heparin)
- Any grade arterial thromboembolic event
- Grade 3congestive heart failure
- Gastrointestinal perforation
- Wound dehiscence requiring medical or surgical intervention
- Inability of subject to comply with study requirements
- Determination by the investigator that it is no longer safe for the subject to continue therapy
- All Grade 4 events thought to be related to bevacizumab by the investigator

Patients who have an ongoing bevacizumab-related Grade 4 or serious adverse event at the time of discontinuation from study treatment will continue to be followed until resolution of the event or until the event is considered irreversible.

Patients with skin metastases that begin to bleed while on study should have the bevacizumab discontinued and can continue with ipilimumab as long as the patient continues to meet all other treatment criteria.

6.2 Ipilimumab Dose Modifications and Toxicity Management

Dose reductions to ipilimumab within a cohort will not be allowed. Modifications to the dosing schedule are listed below.

Treatment modifications will be made based on specified safety criteria. Patients will delay or discontinue treatment with ipilimumab if they experience at least one adverse event, specified below, considered by the Investigator to be **"possibly", probably" or "certainly" related to ipilimumab treatment.**

The following criteria will be used to determine dosing delay, restarting doses, or discontinuing ipilimumab.

- ***Note that dose <u>reductions</u> are <u>not</u> allowed; ipilimumab must be administered at the assigned dose for each cohort.***

Delay ipilimumab dosing for the following related adverse event(s):

- Any Grade 2 or greater non-skin related adverse event (including IRAEs);
- Any Grade 3 or greater skin-related adverse event (including IRAEs) regardless of causality

Restart ipilimumab dosing if/ when the adverse event(s) resolve(s) to ≤ Grade 1 severity or returns to baseline within 3 weeks of initial dose administration:

- If the *adverse event has resolved,* restart ipilimumab dosing at the next scheduled 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 *omitted*.

Any IRAE of grade 3 or higher that is believed to be "possibly", probably" or "certainly" related to ipilimumab treatment and is not effectively managed with local or systemic immunosuppression within 7 days, will be considered a DLT.

For patients treated in the MTD-expansion cohort, or enrolled to cohorts 3 and 4, IRAEs that resolve to ≤ grade 1 any time prior to the planned next dose of treatment may continue with treatment as long as the patient has not required more than 2 weeks of systemic steroids (excluding endocrine replacement). If IRAE has not resolved to ≤ grade 1 before the next planned treatment, the patient may miss one cycle and be treated at the next scheduled cycle if the IRAE resolves to ≤ grade 1 as long as the patient has not required more than 2 weeks of systemic steroids (excluding endocrine replacement). If the IRAE has not resolved by that time, the patient should not receive further treatment on study.

If it is necessary to increase a steroid dose to 240 mg in order to treat the IRAE or a participant requires a dose of 120 mg maintenance dose for at least 2 weeks to manage the IRAE, this will be considered a DLT. Please refer to the algorithms in appendices for guidance on steroid doses to manage immune toxicities.

DLT will include any expected toxicity of Grade 3 or higher, believed to be "possibly", probably" or "certainly" related to ipilimumab <u>and/or bevacizumab</u> treatment outlined in the

Dose Modification and Toxicity Management section of this protocol, that is not effectively managed according to the rules of the Dose Modification and Toxicity Management section.

Discontinuation of Therapy

Study therapy MUST be immediately discontinued for the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event, laboratory abnormality or intercurrent illness which, in the opinion of the Investigator, indicates that continued treatment with study therapy is not in the best interest of the subject
- Pregnancy

6.3 Continuation of Single Drug Once DLT Resolved to < Grade 2

The nature of the DLTs will determine dose modifications. If DLT occurs that is related to bevacizumab (e.g. unacceptable hypertension) that is refractory to dosing delays or other intervention, then bevacizumab will be discontinued, but ipilimumab may continue at the dose and schedule of the cohort as long as all other treatment eligibility criteria continue to be met and all toxicities have resolved to < grade 2 unless removal of the patient from study is otherwise specified in above section 6.0. Participants that discontinue from bevacizumab that continue to be treated with ipilimumab will come to clinic every 4 weeks for safety assessments, and receive ipilimumab every 12 weeks.

If expected DLTs from ipilimumab occur (e.g. colitis), then the ipilimumab will be discontinued and bevacizumab may be continued as long as all other treatment eligibility criteria continue to be met and all toxicities have resolved to < grade 2. All grade 4 IRAEs thought to be possibly, probably, or certainly related to ipilimumab will be considered DLTs.

6.3.1 Permanent Discontinuation of Ipilimumab

Permanent Discontinuation of ipilimumab for related adverse events

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

- Any ≥ Grade 3 bronchospasm or other hypersensitivity reaction;
- Any other ≥ Grade 3 non-skin related adverse event with the exception of events listed under "No Discontinuation" (below);
- Any adverse event, laboratory abnormality or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the patient with continued dosing.

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

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event, laboratory abnormality or intercurrent illness which, in the opinion of the Investigator, indicates that continued treatment with study therapy is not in the best interest of the subject
- Pregnancy
  - 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 Bristol-Myers Squibb.
- Imprisonment or the compulsory detention for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

Exceptions to Permanent Discontinuation of ipilimumab under the following situations:

- 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.

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, hypo- or hypertension, bronchospasm or other symptoms. No prophylactic pre-medication will be given unless indicated by previous experience in an individual patient.

Reactions should be treated based upon the following recommendations:

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

- Decrease the rate of infusion until recovery from symptoms, remain at bedside and monitor patient;
- Complete the ipilimumab infusion at the initial planned rate ;
- Diphenhydramine 50 mg 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 moderate symptoms (any symptom not listed above (mild symptoms) or below (severe symptoms) such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic BP >80 mmHg):
  - Interrupt ipilimumab;
  - Administer diphenhydramine 50 mg IV;
  - Monitor patient closely until resolution of symptoms;
  - Corticosteroids may abrogate any beneficial immunologic effect, but may be administered at the discretion of the treating physician;
  - Resume ipilimumab infusion after recovery of symptoms;
  - At the discretion of the treating physician, ipilimumab infusion may be resumed at *one half the initial infusion rate, then increased incrementally to the initial infusion rate.*
  - If symptoms develop after resumption of the infusion, the infusion should be discontinued and no additional ipilimumab should be administered that day;

- The next dose of ipilimumab will be administered at its next scheduled time and may be given with pre-medication (diphenhydramine and acetaminophen) and careful monitoring, following the same treatment guidelines outlined above;
- At the discretion of the treating physician additional oral or IV antihistamine may be administered prior to dosing with ipilimumab.

- For severe symptoms (e.g., any reaction such as bronchospasm, generalized urticaria, systolic blood pressure <80 mm Hg, or angioedema):
  - Immediately discontinue infusion of ipilimumab, and disconnect infusion tubing from the subject;
  - Consider bronchodilators, epinephrine 1 mg IV or subcutaneously, and/or diphenhydramine 50 mg IV, with solumedrol 100 mg IV, as needed.
  - Patients should be monitored until the Investigator is comfortable that the symptoms will not recur;
  - No further ipilimumab will be administered;

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

6.4 Treatment of Ipilimumab Related Isolated Drug Fever

In the event of isolated drug fever, the Investigator must use clinical judgment to determine if the fever is related to the ipilimumab or to an infectious etiology.

If a patient experiences isolated drug fever, for the next dose, pre-treatment with acetaminophen or non-steroidal anti-inflammatory agent (Investigator discretion) should be institute 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 pre-medication and post dosing with an appropriate antipyretic, the infusion rate for subsequent dosing should be decreased to 50% of the previous rate. If fever recurs following infusion rate change, the Investigator should assess the patient's level of discomfort with the event and use clinical judgment to determine if the patient should receive further ipilimumab.

6.5 Immune Related Adverse Events (IRAEs): Definition, Monitoring, Treatment

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

For the purposes of this study, an IRAE is defined as an AE of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an 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 CRF.

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

It is unknown if systemic corticosteroid therapy has an attenuating effect on ipilimumab activity. However, clinical anti-tumor responses have been maintained in patients treated with corticosteroids and discontinued from ipilimumab. If utilized, corticosteroid therapy should be individualized for each patient. Prior experience suggests that colitis manifested as ≥ Grade 3 diarrhea requires corticosteroid treatment. See Appendix 1 for additional details.

7.0 STUDY MEDICATIONS

7.1 BEVACIZUMAB FORMULATION

Bevacizumab is a clear to slightly opalescent, colorless to pale brown, sterile liquid concentrate for solution for intravenous (IV) infusion. Bevacizumab may be supplied in 5-cc (100-mg), and 20-cc (400-mg) glass vials containing 4 mL or 16 mL, of bevacizumab, respectively (all at 25 mg/mL). Vials contain bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile

Water for Injection (SWFI), USP. Vials contain no preservative and are suitable for single use only.

For further details and molecule characterization, see the bevacizumab Investigator Brochure.

Bevacizumab Storage

Upon receipt of the study drug, vials are to be refrigerated at 2°C–8°C (36°F–46°F) and should remain refrigerated until just prior to use. DO NOT FREEZE. DO NOT SHAKE. Vials should be protected from light.

Opened vials must be used within 8 hours. VIALS ARE FOR SINGLE USE ONLY. Vials used for 1 subject may not be used for any other subject. Once study drug has been added to a bag of sterile saline, the solution must be administered within 8 hours.

7.2 Ipilimumab Formulation

Investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in the study, whether blinded or unblinded.

Investigational Product Identification

Table 3 : Investigational Drug Information

Unit	Route	Appearance
Ipilimumab 5mg/ml	IV Infusion	Clear, colorless solution in a 10 ml vial or 40 ml vial

Packaging and Labeling

BMS will provide ipilimumab at no cost for this trial.

Study medication will be provided as open-label containers. The labels will contain the protocol prefix, batch number, content, storage conditions and dispensing instructions along with the Investigational New Drug (IND) caution statement.Ipilimumab will be supplied at a concentration of 5 mg/mL in vials containing 10 ml or 40 mL solution.

Storage, Handling, and Dispensing of Ipilimumab

Storage

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

Ipilimumab injections may be stored undiluted (5mg/ml) or following dilution in 0.9% sodium chloride injection (USP) in infusion bags for up to 3 hours at room temperature/under room light or refrigerated (2°C to 8°C) for up to 24 hours.

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

Handling and Disposal

As with all injectable drugs, care should be taken when handling and preparing ipilimumab. Whenever possible, ipilimumab should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents applying aseptic technique. Latex gloves are required.

If ipilimumab concentrate or solution comes in contact with skin or mucosa, immediately and thoroughly wash with soap and water.

After final drug reconciliation, unused ipilimumab solution should be disposed at the site following procedures for the disposal of anticancer drugs.

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

Drug Ordering and Accountability

Following submission and approval of the required regulatory documents, a supply of ipilimumab may be ordered from BMS. Investigators must complete a Drug Request Form and email it to (lisa.hribko@bms.com). Please FAX to (203) 677-6489 (U.S.) if you cannot send the form electronically.

Ipilimumab vials (10 mL and 40mL) are shipped in quantities of ten. Allow 5 business days for shipment of drug from BMS receipt of the ipilimumab Clinical Supply Shipment Request form. Drug is protocol specific, but not patient specific.

All product will be shipped via Federal Express in a temperature-controlled container. Shipments will be made from BMS on Monday through Thursday for delivery onsite Tuesday through Friday. There will be no weekend or holiday delivery of drugs. It is possible that sites may have more than one ipilimumab clinical study ongoing at the same time. It is imperative that only product designated for this protocol number be utilized for this study. To help segregate product for this study from other investigational or marketed product, stickers bearing the BMS protocol number will be provided and should be affixed to the front of the outer carton just above the company names so as not to obscure any marking.

Resupply

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

Ipilimumab Accountability

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

- Amount received and placed in storage area.
- Amount currently in storage area.
- Label ID number or batch number and use date or expiry date.

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

Destruction of Ipilimumab

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

Preparation of Ipilimumab for Infusion

Ipilimumab injection can be used for intravenous (IV) administration without dilution after transferring to a DEHP (di-(2-ethylhexyl)phthalate)-free IV infusion bag (Baxter Intra Via or equivalent). For lower doses (less than 5mg/kg), the drug is diluted with 0.9% sodium chloride injection (USP) to the appropriate concentration (not lower than 0.25 mg/ml) up to a total volume of 90 ml. The product must be infused using a volumetric pump at the protocol-specific dose(s) and rate(s) through a DEHP and latex-free IV transfer set (B. Braun # V 1921 or equivalent) with a 1.2 um in-line filter (B. Braun # FE1212F Filterflow filter extension set). Ipilimumab injection must not be administered as an IV push or bolus injection. Care must be taken to assure sterility of the prepared solutions, since the drug product does not contain any antimicrobial preservatives or bacteriostatic agents.

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.

8.0 Study Procedures and Observations

8.1 SCHEDULE OF EVENTS/REQUIRED DATA

TEST OR PROCEDURE	SCREEN Days –21 To Day 0[C]	PRE-INFUSION [H] Day 1 of every 3 week cycle	DURING IPILIMUMAB INFUSION [E]	Every 6 Weeks (Weeks 7, 13, 19, etc)	Week 8 and Week 16 Only	Week 12 and Every 12 Weeks while on study
Consent	X					
Physical Exam[D]	X	X				
ECOG PS	X	X				
Vital Signs	X	X	X			
EKG	X					
Pregnancy Test (If Indicated) [A]	X	X				
HIV, Hepatitis C Antibody, Hepatitis B Surface Antigen	X					
CBC with diff	X	X				
Serum Chemistries	X	X				
Lipase, Amylase	X	X				
Urinalysis including dipstick[B]	X	X		X		
Urine Protein Creatinine Ratio[B]	X	X		X		
ANA, RF, TSH, anti-thyroglobulin antibodies	X			X		
IF ANA POSITIVE - Anti-DNA antibody, Anti-SSA antibody, Anti-SSB antibody, Anti-LKM antibody, Anti-phospholipid antibody, Anti-islet cell antibody, Anti-neutrophil antibdoy, C3, C4, CH50	X			X		
Research Blood Samples	X			X		
Research Urine Samples [F]	X			X		
Biopsy of site(s) of disease [C]						X One time only
Chest, Abdomen and Pelvic CTs [G]	X					X
Head MRI[D]	X					X
PET Imaging	X				X	

[A]Women of child-bearing potential must have a negative serum β-HCG pregnancy test during screening and a negative urine β-HCG pregnancy test within 24 hours of starting treatment.
[B]Proteinuria will be monitored by dipstick and urine protein:creatinine ratio prior to treatment and at least every six weeks. If appropriate, 24 hour urine collection for protein may be obtained. Participants may be dosed prior to resulting urine protein:creatine ratio if the urine protein on dipstick is less than 2+. Participants that exhibit 2+ or greater proteinuria on dipstick analysis shall not be dosed until the urine protein:creatinine ratio is resulted and within range.
[C]Whenever possible biopsy of site(s) of pre-existing disease will be performed. Post-treatment biopsies, if obtained, should be performed following the induction phase (>12 weeks from start of treatment). While on treatment, biopsies should try to be either small incisional/excisional or core biopsies and occur >14 days from last dose of bevacizumab. If for any reason removal of tissue requires a greater procedure, the biopsy must be done >28 days from the last and >7 days from next dose of bevacizumab. In the maintenance phase, patients may miss one dose of bevacizumab in order to obtain biopsy material if it is felt in the opinion of the treating physician a safety priority.
[D]Head CT may be substituted only if patient cannot tolerate head MRI
[E] Vital signs will be obtained 30, 60 and 90 Minutes after the start of the Ipilimumab infusion or every 30 minutes until the infusion is complete. Vital signs should be obtained 1 hour after the infusion is complete.
[F i]Samples will be obtained from enrolled subjects during the screening period and every 6 weeks, as long as they remain on the trial. Please see section 8.3 and appendix 7 for further information on specimen collection.
[G] Optional CT perfusion scans should be completed at baseline, at the first restaging (week 12), and at the second restaging (week 24). (CT perfusion scans will be performed at DFCI for patients that consent to the optional scan.)
[H] During the induction phase, Ipilimumab and Bevacizumab will be infused during week 1, week 4, week 7, and week 10. For participants that remain on study following induction, Bevacizumab will then be continued every 3 weeks (i.e. week 13, week 16, and week 19). Twelve weeks after the last induction infusion, on week 22, participants will receive the first maintenance dose of Ipilimumab in conjunction with Bevacizumab.

Participants that Discontinue Bevacizumab and Receive Ipilimumab Maintenance Only

TEST OR PROCEDURE	Every 4 Weeks (Between Ipilimumab Doses)	PRE-IPILIMUMAB INFUSION [H] (Every 12 weeks in Maintenance)	DURING IPILIMUMAB INFUSION [E]	Every 8 Weeks	Week 8 and Week 16 Only	Week 12 and Every 12 Weeks while on study
Physical Exam[D]	X	X				
ECOG PS	X	X				
Vital Signs	X	X	X			
Pregnancy Test (If Indicated) [A]	X	X				
CBC with diff	X	X				
Serum Chemistries	X	X				
Lipase, Amylase	X	X				
Urinalysis including dipstick[B]	X	X				
Urine Protein Creatinine Ratio[B]	X	X				
ANA, RF, TSH, anti-thyroglobulin antibodies				X		
IF ANA POSITIVE - Anti-DNA antibody, Anti-SSA antibody, Anti-SSB antibody, Anti-LKM antibody, Anti-phospholipid antibody, Anti-islet cell antibody, Anti-neutrophil antibdoy, C3, C4, CH50				X		
Research Blood Samples				X		
Research Urine Samples [F]				X		
Biopsy of site(s) of disease [C]						X One time only
Chest, Abdomen and Pelvic CTs [G]						X
Head MRI[D]						X
PET Imaging					X	

[A]Women of child-bearing potential must have a negative serum β-HCG pregnancy test during screening and a negative urine β-HCG pregnancy test within 24 hours of starting treatment.

[B]Proteinuria will be monitored by dipstick and urine protein:creatinine ratio prior to treatment and at least every four weeks. If appropriate, 24 hour urine collection for protein may be obtained. Participants may be dosed prior to resulting urine protein:creatine ratio if the urine

protein on dipstick is less than 2+. Participants that exhibit 2+ or greater proteinuria on dipstick analysis shall not be dosed until the urine protein:creatinine ratio is resulted and within range.
[C]Whenever possible biopsy of site(s) of pre-existing disease will be performed. Post-treatment biopsies, if obtained, should be performed following the induction phase (>12 weeks from start of treatment). While on treatment, biopsies should try to be either small incisional/excisional or core biopsies and occur >14 days from last dose of bevacizumab. If for any reason removal of tissue requires a greater procedure, the biopsy must be done >28 days from the last and >7 days from next dose of bevacizumab. In the maintenance phase, patients may miss one dose of bevacizumab in order to obtain biopsy material if it is felt in the opinion of the treating physician a safety priority.
[D]Head CT may be substituted only if patient cannot tolerate head MRI
[E] Vital signs will be obtained 30, 60 and 90 Minutes after the start of the Ipilimumab infusion or every 30 minutes until the infusion is complete. Vital signs should be obtained 1 hour after the infusion is complete.
[F i]Samples will be obtained from enrolled subjects during the screening period and every 6 weeks, as long as they remain on the trial. Please see section 8.3 and appendix 7 for further information on specimen collection.
[G] Optional CT perfusion scans should be completed at baseline, at the first restaging (week 12), and at the second restaging (week 24). (CT perfusion scans will be performed at DFCI for patients that consent to the optional scan.)
[H] During the induction phase, Ipilimumab and Bevacizumab will be infused during week 1, week 4, week 7, and week 10. For participants that remain on study following induction, Bevacizumab will then be continued every 3 weeks (i.e. week 13, week 16, and week 19). Twelve weeks after the last induction infusion, on week 22, participants will receive the first maintenance dose of Ipilimumab in conjunction with Bevacizumab.

8.2 PRE-TREATMENT EVALUATIONS

- Vital signs, including blood pressure
- Urine protein: creatinine ratio or urine dipstick (and 24 hour collection if indicated)

As soon as a patient is considered for this study and prior to any study procedures, the patient will have the nature of the study explained to him or her, and will be asked to give written informed consent and HIPAA authorization (if appropriate). Informed consent must be obtained prior to any procedures that do not constitute part of the patient's normal care.

All Screening diagnostic imaging should be performed within 21 days prior to the first treatment.

A detailed Medical History will be obtained at screening. Please include in history any toxicities related to previous treatments if applicable.

If the screening physical is to conducted within 24 hours of dosing on Day 1, then a single examination may count as both the Screening and pre-dose evaluation.

All patients must have a pre-dosing weight taken at every visit, as appropriate.

8.3 EVALUATIONS DURING TREATMENT

Safety Evaluation

Subjects will be evaluated for safety if they have received any treatment. Adverse events and other symptoms will be graded according to National Cancer Institute's Common Toxicity Criteria for Adverse Events version 3.0 (CTCAE v3). Additionally, serious adverse events (SAE) will be reporting from the time of consent forward for all patients.

A number of measures will be taken to ensure the safety of patients participating in this trial. These measures will be addressed through exclusion criteria and routine monitoring as follows.

Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, blood pressure, and laboratory measurements. Patients will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study. Specific monitoring procedures are as follows:

Vital Signs

Blood pressure, heart rate, and temperature will be obtained as outlined.

During ipilimumab infusions, vital sign measurements (pulse and systolic and diastolic BP) must be collected prior to dosing, every 30 minutes for the duration of the infusion and 1 hour following completion of the infusion.

Orthostatic (supine and standing) BP and heart rate are to be measured when clinically indicated (e.g., experiencing lightheadedness, dizziness, syncope).

Hypertension will be monitored through routine evaluation of blood pressure prior to each bevacizumab treatment. Optimal control of blood pressure according to standard public health guidelines is recommended for patients on treatment with or without bevacizumab.

Procedures During Study

If patients on treatment with bevacizumab require elective major surgery, it is recommended that bevacizumab be held for 4-8 weeks prior to the surgical procedure. Patients undergoing a major surgical procedure should not begin/restart bevacizumab until 4 weeks after that procedure (in the case of high risk procedures such as liver resection, thoracotomy, or neurosurgery, it is recommended that chemotherapy be restarted no earlier than 6 wk and bevacizumab no earlier than 8 wk after surgery).

ECOG Status

ECOG performance status will be evaluated and documented at Screening and at each visit

Laboratory Test Assessments

Serum Chemistry

Serum Chemistry is to be obtained as outlined in Table. Serum chemistry tests are to include: albumin, amylase, lipase, BUN, creatinine, ALT, AST, LDH, serum alkaline phosphatase, direct and total bilirubin, glucose, total protein, sodium, potassium, chloride, HCO3, calcium, and uric acid.

Hematology

A CBC with differential is to be obtained as outlined in Table. The CBC with differential includes: hemoglobin, hematocrit, white blood cells, platelets, neutrophils, lymphocytes, eosinophils and monocytes. Additional draws must be incorporated when monitoring recovery from any hematologic AE.

Urinalysis

A urinalysis will be obtained as outlined in Table 4 Scheduled Events/Required Data and will include a gross examination including: specific gravity, protein, glucose and blood. A microscopic evaluation will also be performed, as needed, to include WBC/HPF, RBC/HPF and any additional findings.

Proteinuria will be monitored by urine protein:creatinine (UPC) ratio every 3 weeks and at least every 6 weeks.

HIV and Hepatitis Panel

At screening, testing should be performed for HIV, hepatitis C antibody and HBsAg utilizing local standard informed consent procedures prior to this laboratory collection.

Imaging

Patients will undergo diagnostic imaging as outlined in Table of Required Data.

Response and treatment evaluations will be made with CT and MRI imaging.

PET imaging is utilized to assess for metabolic changes as a function of this novel combination therapy at baseline and over the first sixteen weeks.

IMMUNE RELATED (IR) CLINICAL RESPONSE CRITERIA (irRC)

The sum of the products of diameters at tumor assessment using the irRC criteria for progressive disease-incorporates the contribution of new measurable lesions. Each net Percentage Change in

Tumor Burden per assessment using irRC criteria accounts for the size and growth kinetics of both old and new lesions as they appear.

Definition of Index Lesions Response using irRC

- irComplete Response (irCR): Complete disappearance of all *index* lesions. This category encompasses exactly the same subjects as "CR" by the mWHO criteria.
- irPartial Response (irPR): Decrease, relative to baseline, of 50% or greater in the sum of the products of the two largest perpendicular diameters of all *index* and all new measurable lesions (ie., Percentage Change in Tumor Burden). Note: the appearance of new measurable lesions is factored into the overall tumor burden, but does not automatically qualify as progressive disease until the SPD increases by ≥25% when compared to SPD at nadir.
- irStable Disease (irSD): Does not meet criteria for irCR or irPR, in the absence of progressive disease.
- irProgressive Disease (irPD): At least 25% increase Percentage Change in Tumor Burden (i.e., taking sum of the products of all *index* lesions and any new lesions) when compared to SPD at nadir.

Definition of Non-Index Lesions Response using irRC

- irComplete Response (irCR): Complete disappearance of all *non-index* lesions. This category encompasses exactly the same subjects as "CR" by the mWHO criteria.
- irPartial Response (irPR) or irStable Disease (irSD): *non-index* lesion(s) are not considered in the definition of PR, these terms do not apply.
- irProgressive Disease (irPD): Increases in number or size of *non-index* lesion(s) does not constitute progressive disease unless/until the Percentage Change in Tumor Burden increases by 25% (i.e., the SPD at nadir of the index lesions increases by the required amount).

Impact of New Lesions on irRC

New lesions in and by themselves do not qualify as progressive disease. However their contribution to total tumor burden is included in the SPD which in turn feeds into the irRC criteria for tumor response. Therefore, new non-measurable lesions will not discontinue any subject from the study.

Definition of Overall Response Using irRC Criteria Will Be Based on the Following Criteria:

- Immune-related Complete Response (irCR): Complete disappearance of *all* tumor lesions (index and nonindex together with no new measurable/unmeasurable lesions) for at least 4 weeks from the date of documentation of complete response.
- Immune-related Partial Response (irPR): The sum of the products of the two largest perpendicular diameters of all index lesions is measured and captured as the SPD baseline. At each subsequent tumor assessment, the sum of the products of the two largest perpendicular diameters of all index lesions and of new measurable lesions are added together to provide the Immune Response Sum of Product Diameters (irSPD). A decrease, relative to baseline of the irSPD compared to the previous SPD baseline, of 50% or greater is considered an immune Partial Response (irPR).
- Immune-related Stable Disease (irSD): irSD is defined as the failure to meet criteria for immune complete response or immune partial response, in the absence of progressive disease.
- Immune-related Progressive Disease (irPD): It is recommended in difficult cases to confirm PD by serial imaging. Any of the following will constitute progressive disease:
  - At least 25% increase in the sum of the products of all index lesions over baseline SPD calculated for the index lesions.
  - At least a 25% increase in the sum of the products of all index lesions and new measurable lesions (irSPD) over the baseline SPD calculated for the index lesions.

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Table 5: irRC Definitions

Index Lesion Definition	Non-Index Lesion Definition	New measurable Lesions	New unmeasurable Lesions	% change in tumor burden (including measurable new lesions when present)	Overall irWHO Response
Complete Response	Complete Response	No	No	-100%	irCR
Partial Response	Any	Any	Any	≥ -50%	irPR
				<-50% to <+25%	irSD
				>+25%	irPD
Stable Disease	Any	Any	Any	<-50% to <+25%	irSD
				>+25%	irPD
Progressive Disease	Any	Any	Any	≥+25%	irPD

Immune Related Best Overall Response Using irRC (irBOR)

irBOR is the best confirmed irRC overall response over the study as a whole, recorded between the date of first dose until the last TA prior to subsequent therapy (except for local palliative radiotherapy for painful bone lesions) for the individual subject in the study. For the assessment of irBOR, all available assessments per subject are considered.

irCR or irPR determinations included in the irBOR assessment must be confirmed by a second (confirmatory) evaluation meeting the criteria for response and performed no less than 4 weeks after the criteria for response are first met.

STANDARD SOLID TUMOR RESPONSE CRITERIA

Response evaluation criteria in solid tumors

(Adapted from Therasse, Arbuck et al. 2000)

All patients will be scored for standard solid tumor response criteria.

Reporting of Results

All conclusions must be based on all eligible subjects.
Each subject will be assigned to one of the following categories:

- Complete response
- Partial response
- Stable disease
- Progressive disease
- Early death from malignant disease
- Early death from toxicity
- Early death because of other cause, or
- Unknown (not assessable, insufficient data)

Definitions

For Solid Tumors:

Measurable lesions
Lesions that can be measured accurately in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques, or as ≥10 mm with spiral (helical) CT scan.

Nonmeasurable lesions
Lesions not classified as measurable lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan) and truly nonmeasurable lesions.

Target lesions
All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured. Target lesions must be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

Longest diameter for target lesions
The sum of the longest diameter for all target lesions.

Complete Response

Disappearance of all target lesions. Changes in tumor measurements must be confirmed by repeat assessments that must be performed ≥4 weeks after the
criteria for response are first met.

Partial response
At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the screening sum longest diameter. Changes in tumor measurements must be confirmed by repeat assessments that must be performed ≥4 weeks after the criteria for response are first met.

Stable disease
Neither sufficient shrinkage to qualify for partial response nor sufficient increase to quality for progressive disease, taking as reference the smallest sum longest diameter since treatment. Measurements must have met the stable disease criteria at least once ≥4 weeks after treatment.

Progressive disease
At least a 20% increase in the sum of the longest diameter recorded since treatment, or the appearance of one or more new lesions

Non-target lesions
All lesions other than target lesions (or sites of disease) must be identified as nontarget lesions and must be recorded. Measurements of these lesions are not required, but the presence or absence of each must be noted.

Complete response
Disappearance of all nontarget lesions. To be assigned a status of complete response, changes in tumor measurements must be confirmed by repeat assessments that must be performed ≥4 weeks after the criteria for response are first met.

Incomplete response/stable disease
Persistence of one or more nontarget lesion(s). In the case of incomplete response/stable disease, measurements must meet the incomplete response/stable disease criteria ≥4 weeks after treatment.

Progressive disease
Appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions.

Best overall response
The best overall response (modified WHO criteria) is the best response recorded from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the

smallest measurements recorded since treatment). Table 6 provides overall responses for all possible combinations of tumor responses in target and non-target lesions with and without the appearance of new lesions.

Table 6 - Overall responses for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions*

Target lesions	Nontarget lesions	New lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

*CR = complete response: PR = partial response: SD = stable disease and PD = progressive disease.
Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time must be classified as having "symptomatic deterioration."

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

Duration of stable disease
Stable disease is measured from treatment until the criteria for disease progression are met (taking as reference the smallest measurements recorded since the treatment started).

Progression Free Interval
Progression Free Interval is the time from treatment until the time that the criteria for disease progression are observed.

Ipilimumab is expected to trigger immune-mediated responses, which require activation of the immune system prior to the observation of clinical responses. Such immune activation may take weeks to months to be evident. Some patients may have objective volume increase of tumor lesions or other disease parameters (based on study indication) within 12 weeks following start of ipilimumab dosing. Such patients may not have had sufficient time to develop the required immune activation or, in some patients, tumor volume or other disease parameter increases may represent infiltration of lymphocytes into the original tumor or blood. In conventional studies, such tumor volume or relevant laboratory parameter increases during the first 12 weeks of the study would constitute PD and lead to discontinuation of imaging to detect response, thus disregarding the potential for subsequent immune-mediated clinical response. As a result, patients with up to 40% increase in the in the sum of the longest diameter and patients having no more than 2 new target lesions may continue with treatment, as long as they do not have rapid clinical deterioration and will continue to be clinically observed as outlined in the protocol. This will improve the overall assessment of the clinical activity of this treatment and more likely capture its true potential to induce clinical responses.

Correlative Sciences

Correlative studies will be exploratory in nature. All potential biologic effects of the combination of ipilimumab and bevacizumab are not known. This phase I study affords the opportunity to test several likely hypotheses. This will offer insight into the design and implementation of future combination therapies.

Immunogenicity Testing

Development of human anti-human antibodies may be examined. Five (5) mL of blood for HAHA testing may be drawn at regular time intervals as outlined.

Human Leukocyte Antigen Testing

Human leukocyte antigen (HLA) typing may be performed before treatment initiation unless previously obtained. This study is not HLA restrictive. Ten (10) mls of blood may be drawn for HLA-typing.

Paraffin embedded or fresh frozen tissue

When possible, biopsied tissues following the initiation of treatment may be used to obtain tumor infiltrating lymphocytes for determination of T cell populations. Fresh tissue may also be used to obtain mRNA for RT-PCR analyses of cytokines, antigens, immune cells, and vascular targets as well as T cell receptor spectrotying if sufficient materials are available. Paraffin tissues will be used for IHC analyses of lymphocyte populations, cytokine expression and antigen expression. These tissues may be used to stain for immunologic and tumor vascular markers. If available, paraffin embedded tissues from prior biopsies or excisions before treatment may be obtained in order to make comparisons to post-treatment biopsy specimens. No additional pretreatment biopsies will be necessary. There is no requirement for tissue biopsies for patients. Oversight of processing and pathologic review for this study will be performed by Dr. Elsa Velazquez and Dr. Martin Mihm of the Departments of Pathology and Dermatology, Brigham and Women's Hospital and Massachusetts General Hospital.

Post-treatment biopsies, if obtained, should be performed following the induction phase (>12 weeks from start of treatment), although this may vary at the discretion of the treating physician. While on treatment, biopsies should try to be either small incisional/excisional or core biopsies and occur >14 days from last dose of bevacizumab. If for any reason removal of tissue requires a greater procedure, the biopsy must be done >28 days from the last and >7 days from next dose of bevacizumab. In the maintenance phase, patients may miss one dose of bevacizumab in order to obtain biopsy material if it is felt in the opinion of the treating physician a safety priority.

Research Bloods

Serum, plasma, and circulating mononuclear cells will be frozen prior to beginning treatment and at defined intervals thereafter as depicted in the Data Collection table. These samples may be used for future studies to assay the humoral and cellular immune responses and effects on angiogenesis. They will be labeled with protocol number, medical record number, and date of acquisition only.

Research Urine Samples

Matrix metalloproteinsases (MMPs) are zinc dependent proteolytic enzymes (endopeptidases) which have been found to aid melanoma cells in metastasizing by breaking down cells' extracellular matrix and allowing cancer cells to remodel it. MMPs are located on the cell surface and interact with non-matrix proteins such as adhesion molecules, growth factors and mediators of angiogenesis and apoptosis (Hofmann, Biochimie 2005). MMP2 and MMP9 degrade type IV collagen which is a major component of the basement membrane (Liotta (cell) 1991) and both MMP 9 and MMP 2 are known to play a role in the release of vascular endothelial growth factor (VEGF) and the collection of ascites (Belotti 2003). Expression of MM2 in melanoma cells is correlated with extracellular degradation and melanoma growth and spread (Oshishni European J of Derm 2001). In other cancers, MMP levels in blood and urine have been used as a marker for malignant and metastatic phenotype.

The lab of Dr. Marsha Moses at Children's Hospital Boston has reported that MMPs can be detected in the urine of cancer patients and that MMP levels in urine can be correlated with disease status and stage (Moses *et al.,* 1998; Chan *et al,* 2004*;* Smith *et al.,* 2008).Currently, there is no data which correlates urine levels of MMPs to the activity of the tumor vasculature in melanoma. We have been afforded a unique opportunity to work with the Moses lab and prospectively test the predictive value of urine MMP levels and correlate to clinical activity in patient receiving treatment with know anti-VEGF activity.

Urine will be collected to assay for MMPs from patients who enroll on the study in order to determine the pre and post treatment levels of MMPs in subjects with metastatic melanoma who are treated with Sutent (and Ipi / BEV). Please see appendix 3 for further information on the procedure for specimen collection and transport.

Optional CT Perfusion Imaging

CT perfusion imaging has been studied in both human and animal models for several years. With the introduction of newer, faster CT scanners and the use of chemotherapeutic agents that target anti-angiogenesis, the indications for utilizing this technique to detect tumor response, often not visible by conventional CT imaging protocols, is paramount. Although many earlier studies focused on perfusion imaging in the brain (1), more recent studies have looked at perfusion imaging of intrathoracic nodules (2) and tumors elsewhere within the body (3, 4, 5.)

Sahani and Bellomi, in independent studies (3, 4), looked at perfusion imaging of rectal cancers, both prior to, and following treatment with chemotherapy and radiation. Following bolus IV infusion of contrast media, dynamic perfusion imaging was performed for 45-50 sec, and tissue blood flow (BF), blood volume (BV), mean transit time (MTT) and vascular permeability-surface area product (PS) were determined. Both studies documented higher blood flow in tumor compared to normal rectal wall, and a marked decrease in perfusion following therapy.

Sahani has also looked at tumor perfusion imaging of hepatocellular carcinoma, and has reportedly done some work evaluating the effects of the anti-angiogenic agent, bevacizumab in these patients (5, 6.) He reportedly documented decreased blood flow, blood volume and permeability-surface area product in HCC after two weeks of therapy with bevacizumab.

To date, no studies have been published in the radiologic literature evaluating perfusion imaging of melanoma. As proposed, patients will undergo CT scans at baseline, and at week 12 and 24 restaging. At the time of these studies, optional perfusion imaging sequences will be obtained.

A non-contrast enhanced helical CT scan will be acquired as standard of care, to determine the site of tumor involvement to be further evaluated with tumor perfusion imaging. Subsequently, 50-70 cc of non-ionic intravenous contrast will be administered, while a research dynamic perfusion CT scan is acquired through the region of interest. Blood flow (BF), blood volume (BV), mean transit time (MTT) and vascular permeability-surface area product (PS) will be calculated from the CT perfusion images using vendor software. We aim to look at these factors and their magnitude of change over treatment, in an attempt to detect tumor response much earlier than is presently possible, using traditional RECIST criteria in the measurement of morphologic changes.

Following the perfusion sequences, standard clinical chest, abdomen and pelvis CT will be performed, with a reduced contrast dose. Total dose of contrast injected may be increased minimally over standard dose for chest, abdomen and pelvis CT scan (100 cc), though not greater than amount for other scans, ie neck, chest, abdomen and pelvis (150 cc).

A conservative estimate of the maximum additional radiation dose from the perfusion sequences is less than 15 mS.

Exploratory Research

The primary goal of the correlative sciences is to obtain an early gauge of anti-cancer immunological activity and effects on the tumor vasculature of the combination of bevacizumab and ipilimumab. First, we will determine immune responses to known melanoma antigen targets as a function of treatment with bevacizumab and ipilimumab. This will include and not be limited to Mart-1, tyrosinase, gp100, ATP6S1, and ML-IAP. Both humoral and cellular immune responses will be investigated by ELISAs, ELISPOTs, and cytotoxic T cell chromium release assays established in Dr. Hodi's laboratory. If sufficient materials are available, we will investigate the effects on tumor vasculature and vascular active molecules as a function of treatment with bevacizumab and ipilimumab. Studies will include and not be limited to monitoring VEGF, bFGF, and HGF levels. Circulating endothelial cells and progenitors may be studied as a function of treatment. Finally we will attempt to determine the effects of treatment with the combination of bevacizumab and ipilimumab on immune regulatory cell function. VEGF has been shown to suppress immature dendritic cells and ipilimumab is believed to decrease regulatory T cell function. Potential synergies on regulatory cell function will be investigated in pilot studies. These will be performed by phenotyping circulating immune cells by flow cytometry of peripheral blood samples and *in vitro* lymphocyte proliferation assays.

9.0 STATISTICAL METHODS

As of June 2010, patients have safely been treated on cohorts 1 and 2. The first cohort of five patients was enrolled to cohort 1 at the 10mg/kg of Ipilimumab plus 7.5mg/kg Bevacizumab dose level. There were no dose limiting toxicities in this cohort during the 12 week monitoring period. The next cohort of five patients was enrolled to cohort 2 at the 10mg/kg of Ipilimumab plus 15mg/kg Bevacizumab dose level. Cohort 2 enrolled was determined to be the maximum tolerable dose level (10mg/kg of Ipilimumab plus 15mg/kg Bevacizumab) and the expansion cohort of twelve patients began enrolling on 2/16/2010. As of August 2010, 21 participants have enrolled on study: 5 participants to cohort 1, 5 participants to cohort 2, and 11 participants to the dose expansion of cohort 2. There is one additional patient in screening to complete the 12 patient dose expansion currently.

9.1 Populations for Analysis

Enrolled patients: All patients who signed the informed consent document.

MTD-treated patients: All enrolled patients who received at least one dose of the study drug combination at the MTD.

Cohorts 3 and 4: Patients enrolled to two cohorts treated with ipilimumab at 3 mg/kg (12 patients per cohort) and bevacizumab at either 7.5 mg/kg (cohort 3) or 15 mg/kg (cohort 4).

9.2 Endpoints

9.2.1 Primary Endpoint

The primary endpoint in this study is the determination of the maximum tolerated dose (MTD). For each dose cohort, patients will be assessed after 12 weeks of treatment. Patients experiencing rapid disease progression within the first four weeks of treatment will not be classified as having a DLT.

9.2.2 Determination of DLT

Toxicity grading will be according to the NCI Common Toxicity Criteria for Adverse Events (V3.0).

A patient will be classified as having a DLT for any of the following:

(1) An unexpected toxicity of grade 3 or higher,
(2) A toxicity of grade 3 or higher outlined in the Dose Modification and Toxicity Management section of this protocol that is not effectively managed with local or systemic immunosuppression within 7 days,
(3) Eye pain of grade 2 or higher, or uveitis of any grade,
(4) Any grade 4 immunological toxicity related to ipilimumab
(5) Two delays of treatment (not due to scheduling non-compliance) each lasting more than 10 days within 4 cycles of drug.

Since both drugs could potentially cause GI perforation, the MTD will have been reached if two patients in any dose cohort experience GI perforation.

Treatment will begin with doses of bevacizumab at 7.5 mg/kg and ipilimumab at 10 mg/kg, levels that have shown clinical response using each drug alone. If there is a synergistic effect of bevacizumab and ipilimumab at these dose levels resulting in dose-limiting toxicity (DLT), the dose of ipilimumab will be decreased to 3.0 mg/kg, holding the dose of bevacizumab steady. If no DLT is observed, the dose of bevacizumab will be increased to 15 mg/kg while holding the dose of ipilimumab steady. The following design is proposed to determine the maximum tolerated dose (MTD) of bevacizumab plus ipilimumab.

Cohort Dose

Cohort 1: Ipilimumab 10 mg/kg IV doses every 3 weeks x 4 (induction), then every 3 months (maintenance); Bevacizumab 7.5 mg/kg IV every 3 weeks (continuous)

Cohort 2: Ipilimumab 10 mg/kg IV doses every 3 weeks x 4 (induction), then every 3 months (maintenance); Bevacizumab 15 mg/kg IV every 3 weeks (continuous)

Cohort 3: Ipilimumab 3 mg/kg IV doses every 3 weeks x 4 (induction), then every 3 months (maintenance); Bevacizumab 7.5 mg/kg IV every 3 weeks (continuous)

Cohort 4: Ipilimumab 3 mg/kg IV doses every 3 weeks x 4 (induction), then every 3 months (maintenance); Bevacizumab 15 mg/kg IV every 3 weeks (continuous)

Patients will enter each cohort in sets of five, beginning in Cohort 1, and receive four cycles of study drug. If three or more patients experience dose-limiting toxicity (DLT) during the first 12 weeks, Cohort 1 will be determined to have unacceptable toxicity. The next set of five patients will then be enrolled in Cohort 3, which will maintain the dosage of bevacizumab and decrease ipilimumab to 3.0 mg/kg. Enrollment into Cohort 3 will require discussion between the Principal Investigator and Bristol-Myers Squibb (BMS) and written approval from a BMS representative. If there are three or more patients with DLT during the first 12 weeks in Cohort 3, the study will be halted pending further discussion with BMS. Otherwise, the study will continue and enroll the next five patients into Cohort 4, increasing the dose of bevacizumab. If there are three or more patients with DLT in Cohort 4, then Cohort 3 will be the MTD. If the toxicity profile of Cohort 4 is acceptable, it will be the MTD.

If the toxicity profile of Cohort 1 is acceptable, the next set of five patients will be enrolled into Cohort 2, testing the combined effect of both bevacizumab and ipilimumab at high dose levels. If three or more patients experience DLT during the first 12 weeks, Cohort 2 will be determined to have unacceptable toxicity and Cohort 1 will be considered the MTD. Otherwise, the MTD will be Cohort 2.

Before escalation to the next dose level, three patients in a cohort must complete the 12 weeks of induction treatment without dose limiting toxicities.

Progression to either Cohort 2 or Cohort 3 will depend solely upon the toxicity profile observed in Cohort 1; there will be no escalation from Cohort 2 to Cohort 3.

Patients in any cohort exhibiting DLT will not be replaced; however, up to two patients may be replaced in a cohort due to rapid progression of disease within the first four weeks that requires alternative treatment. These patients will not be classified as having a DLT, but will be included in calculations of secondary endpoints.

To ensure that toxicity at the MTD is acceptable and to gain preliminary experience with biologic activity of the two drugs, an additional 12 patients will be accrued at the MTD. The operating characteristics of this design are shown in Table 7.

Table 7 – Probability of Escalation

True (but Unknown) Rate of DLT (%)	Probability of Escalation (%)
5	99.9
10	99.1
20	94.2
30	83.7
40	68.2
50	50.0
60	31.7
70	16.3

Under this design, there is a 94% probability of escalation if the true rate of DLT is no more than 20%. If the true rate of DLT exceeds 50%, the probability of escalation is less than 50%.

Two additional cohorts of 12 patients each will be enrolled to the study to gain biological experience with the combination of ipilimumab at 3 mg/kg, and bevacizumab at either 7.5 mg/kg or 15 mg/kg. The estimation of toxicity rates will be calculated for each cohort (MTD-dosage expansion, cohort 3, cohort 4).

It is estimated that approximately 46 patients will be enrolled in this protocol. This estimate is roughly based on the expectation of studying three dose levels, with an average of 5-7 patients per level, and 12 patients in the expansion cohort of the MTD. Twelve additional patients will be enrolled to cohort 3 followed by 12 patients enrolled in cohort 4 as part of the study amendment.

9.2.2 Secondary Endpoints

Secondary endpoints will be assessed separately for patients in the MTD-treated expansion cohort, cohort 3 or cohort 4, and will be: best overall response rate, disease control rate, time to tumor progression, and duration of response. Exploratory analyses will focus on clinical activity by Immune-Related Criteria.

At the 12-week restaging, patients will be classified as having one of the following according to solid tumor criteria: complete response, partial response, stable disease, progressive disease, death without progression (from toxicity, or due to other, or unknown, causes).

Using the classifications determined at 12-weeks, the best overall response (per modified WHO criteria) will be determined for each patient. Rates will be the proportions with partial response, complete response, stable disease, or progressive disease, and will be calculated using the total number of patients in the respective cohort (MTD-treated, or cohorts 3 or 4) as the denominator.

Disease control rate will be defined as the proportion of patients within each cohort with complete response, partial response, or stable disease. Best overall response rates and disease control rates will be presented by cohort with an associated 95% exact binomial confidence interval. Based upon 12 patients per cohort, the confidence intervals will be no wider than ±0.26.

Time to tumor progression (TTP) will be defined within each cohort as the time between the start of treatment and the date of disease progression. If a patient dies without documented clinical

progression, time to tumor progression will be the time from start of treatment until death. Patients, who have neither progressed nor died, will be censored at the date of last tumor assessment. Duration of response (DoR) will be computed for patients in each of the three cohorts whose best responses were either partial response or complete response and will be defined as the time between the date of first documented response and the date of disease progression. If there is no known date of progression due to death, date of death will be used for date of disease progression. Patients who have neither progressed nor died will be censored at the date of last tumor assessment. The distributions of TTP and DoR times by cohort will be described using the method of Kaplan-Meier. Point estimates of TTP or DoR will be presented with 95% confidence intervals derived using log(-log(survival)) methodology.

Correlative Measures

The primary goal of the correlative sciences is to obtain an early gauge of anti-cancer immunological activity and effects on the tumor vasculature of the combination of bevacizumab and ipilimumab. Analyses are intended to be exploratory in nature. First, we will determine immune responses to known melanoma antigen targets as a function of treatment with bevacizumab and ipilimumab. This will include, but not be limited to Mart-1, tyrosinase, gp100, ATP6S1, and ML-IAP.

If sufficient materials are available, we will investigate the effects on tumor vasculature and vascular active molecules as a function of treatment with bevacizumab and ipilimumab. Studies will include and not be limited to monitoring VEGF, bFGF, and HGF levels. Circulating endothelial cells and progenitors may be studied as a function of treatment. Finally we will attempt to determine the effects of treatment with the combination of bevacizumab and ipilimumab on immune regulatory cell function. VEGF has been shown to suppress immature dendritic cells and ipilimumab is believed to decrease regulatory T cell function.

Percent or fold-changes in melanoma antigen targets, measures of tumor vasculature, circulating endothelial cells or progenitors, or immune regulatory cell function between pre-treatment and the week-12 assessment will be compared, in a pair-wise fashion between the three cohorts using the Wilcoxon rank-sum test. A Bonferroni correction will be used to preserve an overall type I error of 0.10, resulting in a type I error of 0.033 per comparison. Based upon a sample size of 12 patients per group, there will be 80% power to detect differences in median percent change (or fold-change) at least as large as 1.5 times the between-patient standard deviation.

10.0 SAFETY REPORTING OF ADVERSE EVENTS

Adverse Event Monitoring

AEs will be evaluated according to the NCI CTCAE Version 3.0 on a continuous basis starting from when the patient takes the first dose of study administration, up to and including Follow-Up visits (at minimum, for 70 days following last treatment).

SAEs must be collected from the time period following written consent to participate in the study up to and including Follow-Up visits (at minimum, for 70 days following last treatment).

ADVERSE EVENT REPORTING AND DEFINITIONS

Genentech Reporting

In the event of an adverse event the first concern will be for the safety of the subject.

Investigators are required to report to Genentech Drug Safety ANY serious treatment emergent adverse event (STEAE) as soon as possible.

A STEAE is any sign, symptom or medical condition that emerges during Bevacizumab treatment or during a post-treatment follow-up period that (1) was not present at the start of Bevacizumab treatment and it is not a chronic condition that is part of the patient's medical history, OR (2) was present at the start of Bevacizumab treatment or as part of the patient's medical history but worsened in severity and/or frequency during therapy, AND that meets any of the following regulatory serious criteria:

- Results in death
- Is life-threatening
- Requires or prolongs inpatient hospitalization
- Is disabling
- Is a congenital anomaly/birth defect
- Is medically significant or requires medical or surgical intervention to prevent one of the outcomes listed above.

REPORTING OF SERIOUS TREATMENT EMERGENT ADVERSE EVENTS

All STEAEs should be recorded on a MedWatch 3500a Form and faxed to:

Genentech Drug Safety
Fax: (650) 225-4682 or (650) 225-4683

(Please use the safety reporting fax cover sheet attached to this document for your fax transmission)

AND:

F. Stephen Hodi ,M.D.
Dana-Farber Cancer Institute
450 Brookline Ave
Boston, MA 02215
(617) 632-5053
Fax: (617) 582-7992

AND:

Office for the Protection of Research Subjects
Dana-Farber Cancer Institute
20 Overland Street, 2nd Floor
Boston, MA 02115
(617) 632-3029
Fax: (617) 632-2686

MedWatch 3500a Reporting Guidelines:

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500a form:

- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)

- Description of event, severity, treatment, and outcome, if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up information:

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500a report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500a form
- Summarizing new information and faxing it with a cover letter including subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number, if assigned, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted (The subject identifiers are important so that the new information is added to the correct initial report)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the subject for whom and adverse event was reported.

Assessing Causality:

Investigators are required to assess whether there is a reasonable possibility that bevacizumab caused or contributed to an adverse event. The following general guidance may be used.

Yes: if the temporal relationship of the clinical event to bevacizumab administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

No: if the temporal relationship of the clinical event to bevacizumab administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

Safety Reporting Requirements for IND Holders

In accordance with 21 CFR 212.32, sponsor-investigators of studies conducted under an IND must comply with following safety reporting requirements:

a. Expedited IND Safety Reports:

7 Calendar-Day Telephone or Fax Report:

The Sponsor-Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of Bevacizumab. An unexpected adverse event is one that is not already described in the Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event. Each telephone call or fax transmission (see fax number below) should be directed to the FDA new drug review division in the Center for Drug Evaluation and Research or in the product review division for the Center for Biologics Evaluation and Research, whichever is responsible for the review of the IND.

15 Calendar-Day Written Report:

The Sponsor-Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered possibly related to the use of bevacizumab. An unexpected adverse event is one that is not already described in the Investigator Brochure.

Written IND Safety Reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed with the IND concerning similar events should be analyzed. The new report should contain comments on the significance of the new event in light of the previous, similar reports.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech Drug Safety, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500a Form but alternative formats are acceptable (e.g. summary letter).

FDA fax number for IND Safety Reports:

1 (800) FDA - 0178

All written IND Safety Reports submitted to the FDA by the Sponsor-Investigator must also be faxed to: Genentech Drug Safety

Fax: (650) 225-4682 or (650) 225-4683 (Please use the safety reporting fax cover sheet attached to this document for your fax transmission)

AND:

F. Stephen Hodi ,M.D.
Dana-Farber Cancer Institute
450 Brookline Ave
Boston, MA 02215
(617) 632-5053
Fax: (617) 582-7992

AND:

Office for the Protection of Research Subjects
Dana-Farber Cancer Institute
20 Overland Street, 2nd Floor
Boston, MA 02115
(617) 632-3029
Fax: (617) 632-2686

For questions related to safety reporting, contact:

Genentech Drug Safety
Tel: 1-888-835-2555
or
Fax: (650) 225-4682 or (650) 225-4683
(Please use the safety reporting fax cover sheet attached to this document for your fax transmission)

b. IND Annual Reports

In accordance with the regulation 21 CFR § 312.32, the Sponsor-Investigator shall within 60 days of the anniversary date that the IND went into effect submit a brief report of the progress of the investigation. Please refer to Code of Federal Regulations, 21 CFR § 312.32 for a list of the elements required for the annual report. All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. Copies of such reports should be mailed to:

Genentech, Inc.
ATTN: Bevacizumab IST Coordinator
1 DNA Way, Mailstop #59
South San Francisco, CA 94080-4990
Tel: (650) 225-7211

BMS Reporting

Adverse Event Reporting

Collection of Safety Information

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a investigational (medicinal) product (IP), whether or not considered related to the IP.

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

A ***serious AE*** **or reaction** is any untoward medical occurrence that at <u>any dose</u>:

- results in death,

- is life-threatening (defined as an event in which the patient or subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe),
- requires inpatient hospitalization or prolongation of existing hospitalization, (refer to note for exceptions),
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient/subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above.)

NOTE:

- Pregnancy: Incidence of pregnancy is not considered a SAE; pregnancy must, however, be reported immediately to BMS
- Cancer/Overdose: An overdose is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important. For reporting purposes, BMS considers an overdose, regardless of adverse outcome, as an important medical event. All cases of cancer and overdose must be reported immediately to BMS. Determination of seriousness will be reached in consultation with the Safety Physician, Bristol-Myers Squibb Company, Global Pharmacovigilence US Head Quarters or designee
- Hospitalizations (exceptions): Criteria for hospitalizations not reported as SAEs include admissions for:
  - Planned as per protocol medical/surgical procedure
  - Routine health assessment requiring admission for baseline/trending of health status documentation (e.g., routine colonoscopy)
  - Medical/surgical admission for purpose other than remedying ill health state (planned prior to entry into study trial; appropriate documentation required)
  - Admission encountered for other life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g. lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative)

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

Reporting of Serious Adverse Events (SAEs)

Following the subject's written consent to participate in the study, all SAEs should be collected and reported, including those thought to be associated with clinical trial procedures. Following study completion, any SAE thought to be related to study drug or clinical trial procedures should also be reported to BMS.

SAE terminology and severity grading will be based on (i.e CTCAEv3).

The following categories and definitions of causal relationship to study drug should be used for all clinical studies supported by BMS :

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

- Adverse events classified as "serious" require expeditious handling and reporting to BMS to comply with regulatory requirements.
- All SAEs whether related or unrelated to the ipilimumab, must be immediately reported to BMS (by the investigator or designee) within 24 hours of becoming aware of the event. If only limited information is initially available, follow-up reports are required. The original SAE form must be kept on file at the study site.

  All SAEs should be faxed or emailed to BMS at:

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

- For studies conducted under an Investigator IND, any event that is both serious and unexpected must be reported to the FDA as soon as possible and, in no event, later than 7 days (death or life-threatening event) or 15 days (all other SAEs) after the investigator's or

institution's initial receipt of the information. BMS will be provided with a simultaneous copy of all adverse events filed with the FDA. SAEs should be reported on the MedWatch Form 3500A, which can be accessed at: http://www.accessdata.fda.gov/scripts/medwatch/

MedWatch SAE forms should be sent to the FDA at:

MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178 (1-800-332-0178)
http://www.accessdata.fda.gov/scripts/medwatch/

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

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

- Collection of complete information concerning SAEs is extremely important. Full descriptions of each event will be followed by BMS. Thus, follow-up information which becomes available as the SAE evolves, as well as supporting documentation (e.g., hospital discharge summaries and autopsy reports), should be collected subsequently, if not available at the time of the initial report, and immediately sent using the same procedure as the initial SAE report.
- An overdose is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important. For reporting purposes, BMS considers an overdose, regardless of adverse outcome, as an important medical event.
- AEs should be followed to resolution or stabilization, and reported as SAEs if they become serious. This also applies to subjects experiencing AEs that cause interruption or discontinuation of ipilimumab, or those experiencing AEs that are present at the end of their participation in the study; such subjects should receive post-treatment follow-up as appropriate.
- In BMS supported trials, all SAEs must be collected which occur within 30 days of discontinuation of dosing or completion of the patient's participation in the study if the last scheduled visit occurs at a later time. In addition, the Investigator should notify BMS of any SAE that may occur after this time period which they believe to be certainly, probably, or possibly related to ipilimumab.

Pregnancy

Sexually active women of childbearing potential must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized.

Before enrolling women of childbearing potential (WOCBP) in this clinical trial, Investigators must review the guideline about study participation for WOCBP which can be found in the GCP Manual for Investigators. The topics include the following:

- General Information
- Informed Consent Form
- Pregnancy Prevention Information Sheet
- Drug Interactions with Hormonal Contraceptives
- Contraceptives in Current Use
- Guidelines for the Follow-up of a Reported Pregnancy

Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form documenting this discussion.

All WOCBP MUST have a negative pregnancy test within 72 hours prior to receiving ipilimumab. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG. If the pregnancy test is positive, the subject must not receive ipilimumab and must not be enrolled in the study.

In addition, 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.

If following initiation of study treatment, it is subsequently discovered that a trial subject is pregnant or may have been pregnant at the time of ipilimumab exposure, including during at least 6 half-lives after product administration, the ipilimumab will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety). Exceptions to ipilimumab discontinuation may be considered for life-threatening conditions only after consultation with the Principal Investigator or as otherwise specified in this protocol. The Investigator must immediately notify BMS of this event.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the Investigator must report to BMS, and follow-up on information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants should be followed for a minimum of eight weeks.

Reporting of AE Information Following Study Completion

Collection of safety information following the end of investigational product administration is important in assisting in the identification of possible delayed toxicities or withdrawal effects. In this BMS trial with ipilimumab, all SAEs must be collected which occur within 70 days of discontinuation of dosing or completion of the subject's participation in the study if the last scheduled visit occurs at a later time. In addition, the Investigator should notify BMS of any SAE which may occur after this time period which they believe to be certainly, probably or possibly related to investigational product.

A ***serious AE*** **or reaction** is any untoward medical occurrence that at <u>any dose</u>:

- results in death,
- is life-threatening (defined as an event in which the patient or subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe),
- requires inpatient hospitalization or prolongation of existing hospitalization, (refer to note for exceptions),
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient/subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above.)

NOTE:

- Pregnancy: Incidence of pregnancy is not considered a SAE; pregnancy must, however, be reported immediately using the BMS Pregnancy Surveillance Form
- Cancer/Overdose: All cases of cancer and overdose must be reported immediately using the BMS SAE Report Form. Determination of seriousness will be reached in consultation with the Safety Physician, Bristol-Myers Squibb Company, Global Pharmacovigalence US Head Quarters or designee
- Hospitalizations (exceptions): Criteria for hospitalizations not reported as SAEs include admissions for:
  - Planned as per protocol medical/surgical procedure
  - Routine health assessment requiring admission for baseline/trending of health status documentation (e.g., routine colonoscopy)
  - Medical/surgical admission for purpose other than remedying ill health state (planned prior to entry into study trial; appropriate documentation required)
  - Admission encountered for other life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g. lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative)

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

Adverse events classified as "serious" must be recorded on the SERIOUS AE (SAE) page of the CRF and require expeditious handling and reporting to BMS to comply with regulatory requirements. Paper CRFs must be used by all sites to submit SAE data to the sponsor.

All serious AEs whether related or unrelated to investigational product, must be immediately reported to BMS (or designee) by confirmed facsimile transmission and mailing of the completed SAE page (top, white, original). A facsimile transmission does not preclude mailing of the SAE page. Overnight express mail may be used in lieu of facsimile. If only limited information is initially available, follow-up reports are required. In selected circumstances, the protocol may specify conditions which require additional telephone reporting.

Cases of pregnancy must be reported on paper Pregnancy Surveillance Forms in lieu of Collection of complete information concerning SAEs is extremely important. Thus,

follow-up information which becomes available as the SAE evolves, as well as supporting documentation (e.g., hospital discharge summaries and autopsy reports), should be collected subsequently, if not available at the time of the initial report, and immediately sent using the same procedure as the initial SAE report.

In accordance with local regulations, BMS will notify Investigators of all AEs that are serious, unexpected, and certainly, probably, or possibly related to the investigational product or serious reportable adverse events which could be associated with the trial procedures. This notification will be in the form of an Expedited Safety Report (ESR).

Upon receiving such notices, the Investigator must review and retain the ESR with the Investigator Brochure. Where required by local regulations or when there is a central Institutional Review Board (IRB)/Independent Ethics Committee (IEC) for the study, the Sponsor will submit the ESR to the appropriate IRB/IEC. The Investigator and IRB/IEC will determine if the informed consent requires revision. The Investigator should also comply with the IRB/IEC procedures for reporting any other safety information. Where required, submission of ESRs by the Investigator to Health Authorities should be handled according to local regulations.

Periodically, according to the Investigator Brochure SOP, the Investigator Brochure will be updated and include new and relevant safety information. Until such time that an AE becomes identified in the Investigator Brochure, it should be considered unexpected, regardless of whether the AE has been the subject of a previous ESR.

All women of child bearing potential 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.

If following initiation of study treatment, it is subsequently discovered that a trial subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety). Exceptions to investigational product discontinuation may be considered for life-threatening conditions only after consultation with the BMS

Medical Monitor or as otherwise specified in this protocol. The Investigator must immediately notify the BMS Medical Monitor of this event and record the pregnancy on the Pregnancy Surveillance Form. Pregnancy Surveillance Forms are forwarded to BMS.

11.0 DATA AND SAFETY MONITORING

11.1 Data Reporting

11.1.1 Method

The QACT will collect, manage, and monitor data for this study.

11.1.2 Data Submission

The schedule for completion and submission of case report forms (paper or electronic) to the QACT is as follows:

Form	**Submission Timeline**
Eligibility Checklist	Complete prior to registration with QACT
On Study Form	Within 14 days of registration
Baseline Assessment Form	Within 14 days of registration
Treatment Form	Within 10 days of the last day of the cycle
Adverse Event Report Form	Within 10 days of the last day of the cycle
Response Assessment Form	Within 10 days of the completion of the cycle required for response evaluation

Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

11.2 Safety Meetings

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team.

The DSMC will meet quarterly and/or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days for Phase I or II protocols; for gene transfer protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

[delete

11.3 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the Principal Investigator (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

12.0 ADMINISTRATIVE SECTION

Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with Genentech and BMS. The Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an Amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion;
- Bristol-Myers Squibb and Genentech
- Regulatory Authority(ies), if required by local regulations.

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If the revision is an Administrative Letter, Investigators must inform their IRB(s)/IEC(s).

If an Amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the Amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

Investigators must ensure that subjects or their legally acceptable representative are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate.

The following sections contain Bristol-Myers Squibb procedures on obtaining informed consent from subjects prior to participating in a clinical trial.

Informed Consent Procedure

Preparation of the consent form is the responsibility of the Investigator and must include all elements required by ICH, GCP and applicable regulatory requirements, and must adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records. Prior to the beginning of the study, the Investigator must have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects.

The Investigator must provide the subject with a copy of the consent form and written information about the study in the language in which the subject is most proficient. The language must be non-technical and easily understood. The Investigator should allow time necessary for subject to inquire about the details of the study, then informed consent must be signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion. The subject should receive a copy of the signed informed consent and any other written information provided to study subjects prior to subject's participation in the trial.

The informed consent and any other information provided to subjects or the subject's legally acceptable representative, should be revised whenever important new information becomes available that is relevant to the subject's consent, and should receive IRB/IEC approval/favorable opinion prior to use. The Investigator, or a person designated by the Investigator should fully inform the subject or the subject's legally acceptable representative of all pertinent aspects of the study and of any new information relevant to

the subject's willingness to continue participation in the study. This communication should be documented.

During a subject's participation in the trial, any updates to the consent form and any updates to the written information will be provided to the subject.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

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

The Investigator or Sponsor should provide the IRB/IEC with reports, updates and other information (e.g., ESR, Amendments, Administrative Letters) according to regulatory requirements or Institution procedures.

RETENTION OF RECORDS

The Investigator must retain investigational product disposition records, copies of CRFs (paper or electronic files), and source documents for the maximum period required by applicable regulations and guidelines, or Institution procedures, or for the period specified by the Sponsor, whichever is longer.

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APPENDIX 1

SUGGESTED WORK-UP AND TREATMENT FOR IMMUNE RELATED ADVERSE EVENTS (IRAE)S

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

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

Gastrointestinal tract: Diarrhea (defined as either first watery stool, or increase in frequency 50% above baseline with urgency or nocturnal bowel movement, or bloody stool) should be further evaluated and infectious or alternate etiologies ruled out. Patients should be advised to inform the Investigator if any diarrhea occurs, even if it is mild. An algorithm for working up patients with diarrhea or suspected colitis is provided in Appendix 3.

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

exam, to rule out uveitis. Tests should also be performed for WBCs and for stool calprotectin.

Patients with colitis should discontinue any non-steroidal anti-inflammatory medications or any other medications known to exacerbate colitis symptoms. Investigators should use their clinical judgment as to whether corticosteroids are necessary to treat colitis associated with ipilimumab therapy and as to what dose should be used. As guidance prior experience suggests that colitis manifested as ≥ Grade 3 diarrhea requires corticosteroid treatment. For severe symptoms, prednisone 60 mg or equivalent may be required to control initial symptoms and the dose should be gradually tapered over at least one month in duration. Lower doses of prednisone may be considered for less severe cases of colitis. It is suggested that prednisone (for oral administration) or solumedrol (for intravenous administration) be corticosteroid of choice in the treatment of colitis.

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

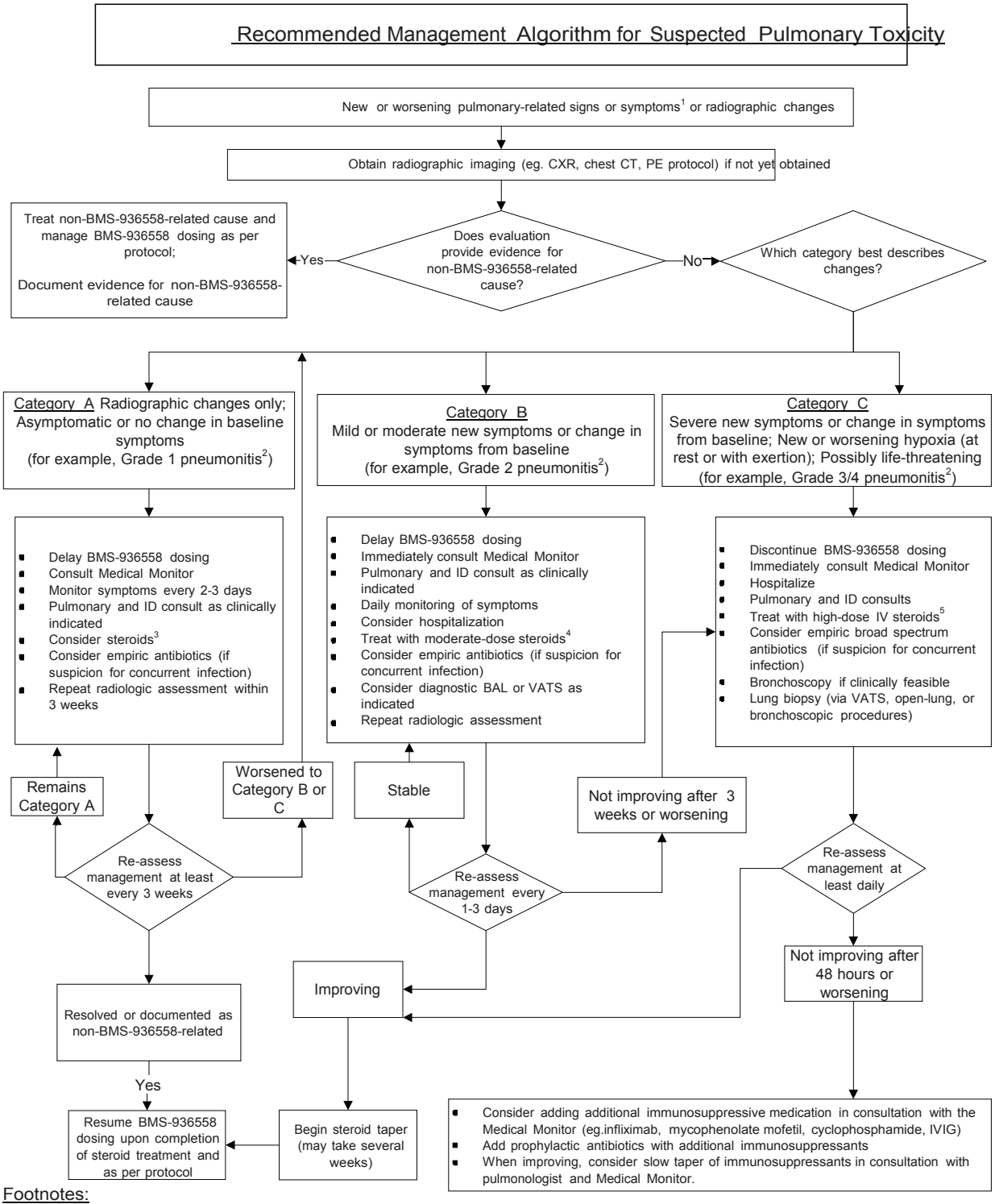
Patients presenting with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have LFTs performed immediately and reviewed before administering the next dose of study drug. Treating physicians should discuss, with the CRO Medical Monitor, unexplained increases in LFTs ≥ 3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

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

Skin: A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be performed if appropriate and if possible, photos of the rash should also be obtained. Low-grade ipilimumab mediated rash and pruritus IRAEs have been treated with symptomatic therapy (e.g., antihistamines). Topical or parenteral corticosteroids may be required for more severe symptoms.

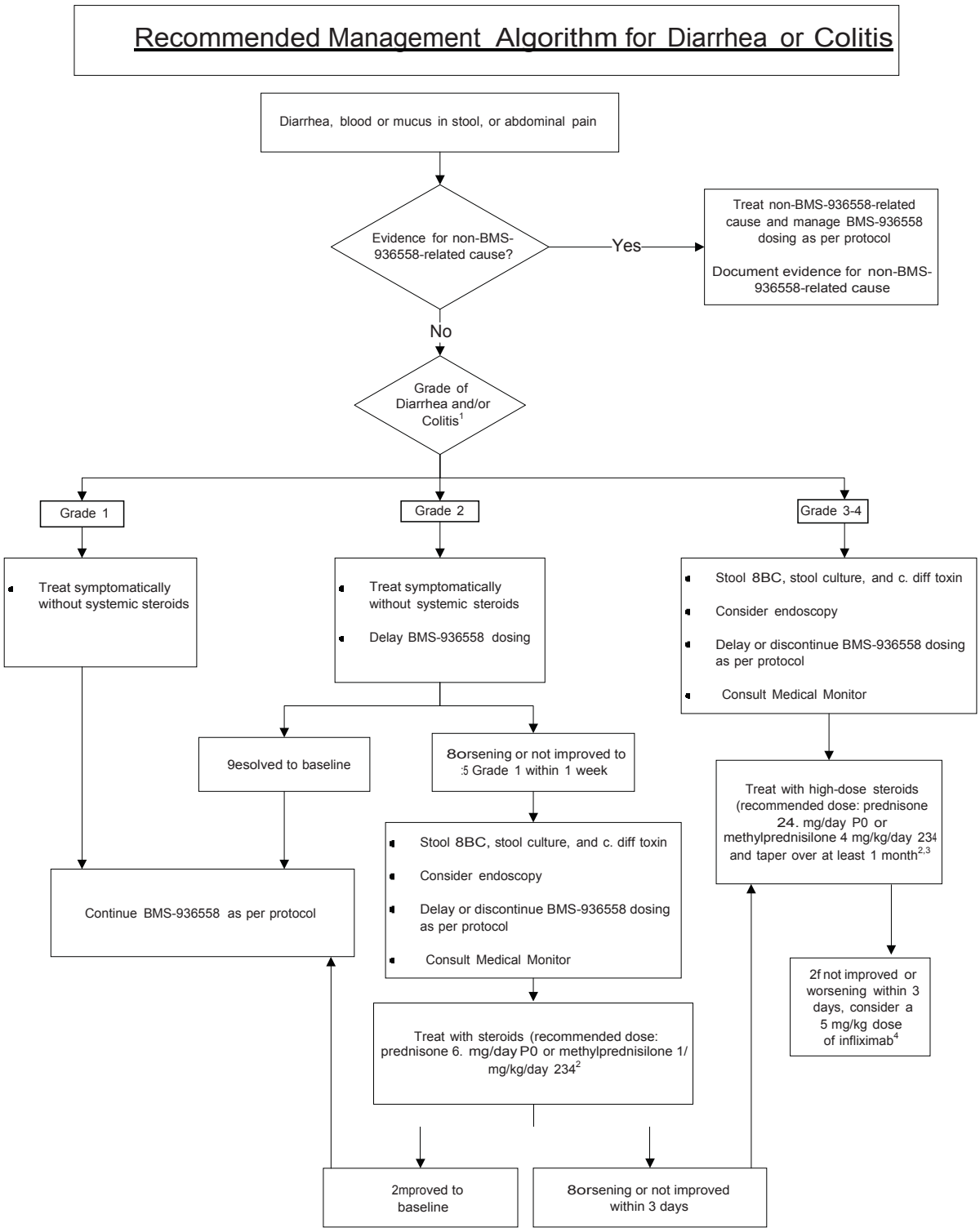
Eye: An ophthalmologist should evaluate visual complaints with examination of the conjunctiva, anterior and posterior chambers and retina; visual field testing and an electroretinogram should also be performed. Patients with ipilimumab related uveitis or episcleritis have been treated with topical corticosteroid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

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


Recommended Management Algorithm for Suspected Pulmonary Toxicity
New or worsening pulmonary-related signs or symptoms[1] or radiographic changes
Obtain radiographic imaging (eg. CXR, chest CT, PE protocol) if not yet obtained
Does evaluation provide evidence for non-BMS-936558-related cause?
Yes
Treat non-BMS-936558-related cause and manage BMS-936558 dosing as per protocol;
Document evidence for non-BMS-936558-related cause
No
Which category best describes changes?
Category A Radiographic changes only; Asymptomatic or no change in baseline symptoms (for example, Grade 1 pneumonitis[2])
Category B Mild or moderate new symptoms or change in symptoms from baseline (for example, Grade 2 pneumonitis[2])
Category C Severe new symptoms or change in symptoms from baseline; New or worsening hypoxia (at rest or with exertion); Possibly life-threatening (for example, Grade 3/4 pneumonitis[2])
Delay BMS-936558 dosing
Consult Medical Monitor
Monitor symptoms every 2-3 days
Pulmonary and ID consult as clinically indicated
Consider steroids[3]
Consider empiric antibiotics (if suspicion for concurrent infection)
Repeat radiologic assessment within 3 weeks
Delay BMS-936558 dosing
Immediately consult Medical Monitor
Pulmonary and ID consult as clinically indicated
Daily monitoring of symptoms
Consider hospitalization
Treat with moderate-dose steroids[4]
Consider empiric antibiotics (if suspicion for concurrent infection)
Consider diagnostic BAL or VATS as indicated
Repeat radiologic assessment
Discontinue BMS-936558 dosing
Immediately consult Medical Monitor
Hospitalize
Pulmonary and ID consults
Treat with high-dose IV steroids[5]
Consider empiric broad spectrum antibiotics (if suspicion for concurrent infection)
Bronchoscopy if clinically feasible
Lung biopsy (via VATS, open-lung, or bronchoscopic procedures)
Remains Category A
Worsened to Category B or C
Stable
Not improving after 3 weeks or worsening
Re-assess management at least every 3 weeks
Re-assess management every 1-3 days
Re-assess management at least daily
Improving
Not improving after 48 hours or worsening
Resolved or documented as non-BMS-936558-related
Yes
Resume BMS-936558 dosing upon completion of steroid treatment and as per protocol
Begin steroid taper (may take several weeks)
Consider adding additional immunosuppressive medication in consultation with the Medical Monitor (eg.infliximab, mycophenolate mofetil, cyclophosphamide, IVIG)
Add prophylactic antibiotics with additional immunosuppressants
When improving, consider slow taper of immunosuppressants in consultation with pulmonologist and Medical Monitor.

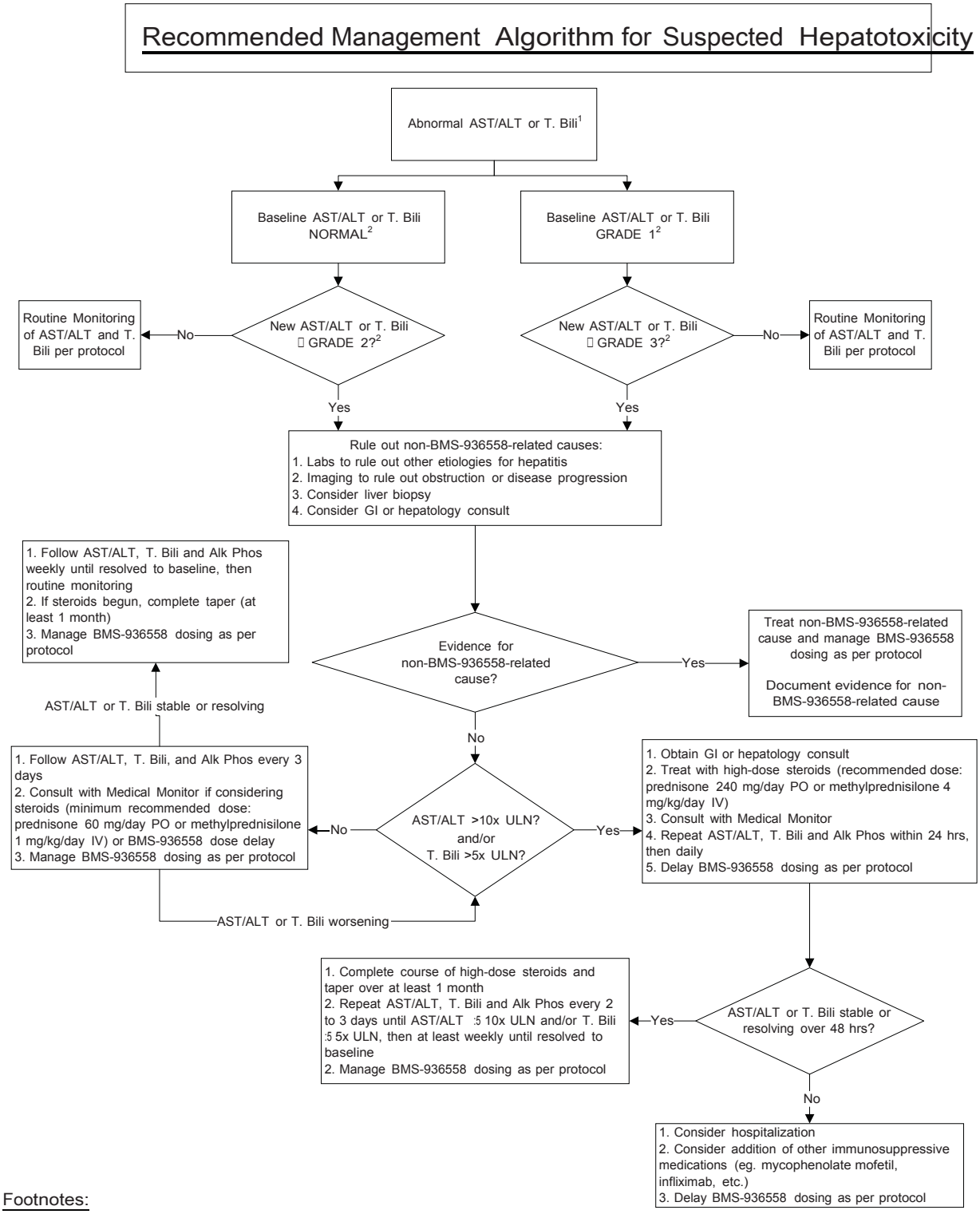
Footnotes:

1. Signs and symptoms include dyspnea, cough, hypoxia, and other respiratory complaints
2. Grading as per NCI CTCAE version 4.0
3. Recommended initial corticosteroid regimen for category A: prednisone 60 mg/day PO or methylprednisilone 1 mg/kg/day IV
4. Recommended initial corticosteroid regimen for category B: prednisone 240 mg/day PO or methylprednisilone 4 mg/kg/day IV
5. Recommended initial corticosteroid regimen for category C: methylprednisilone 1 g/day IV



Footnotes:

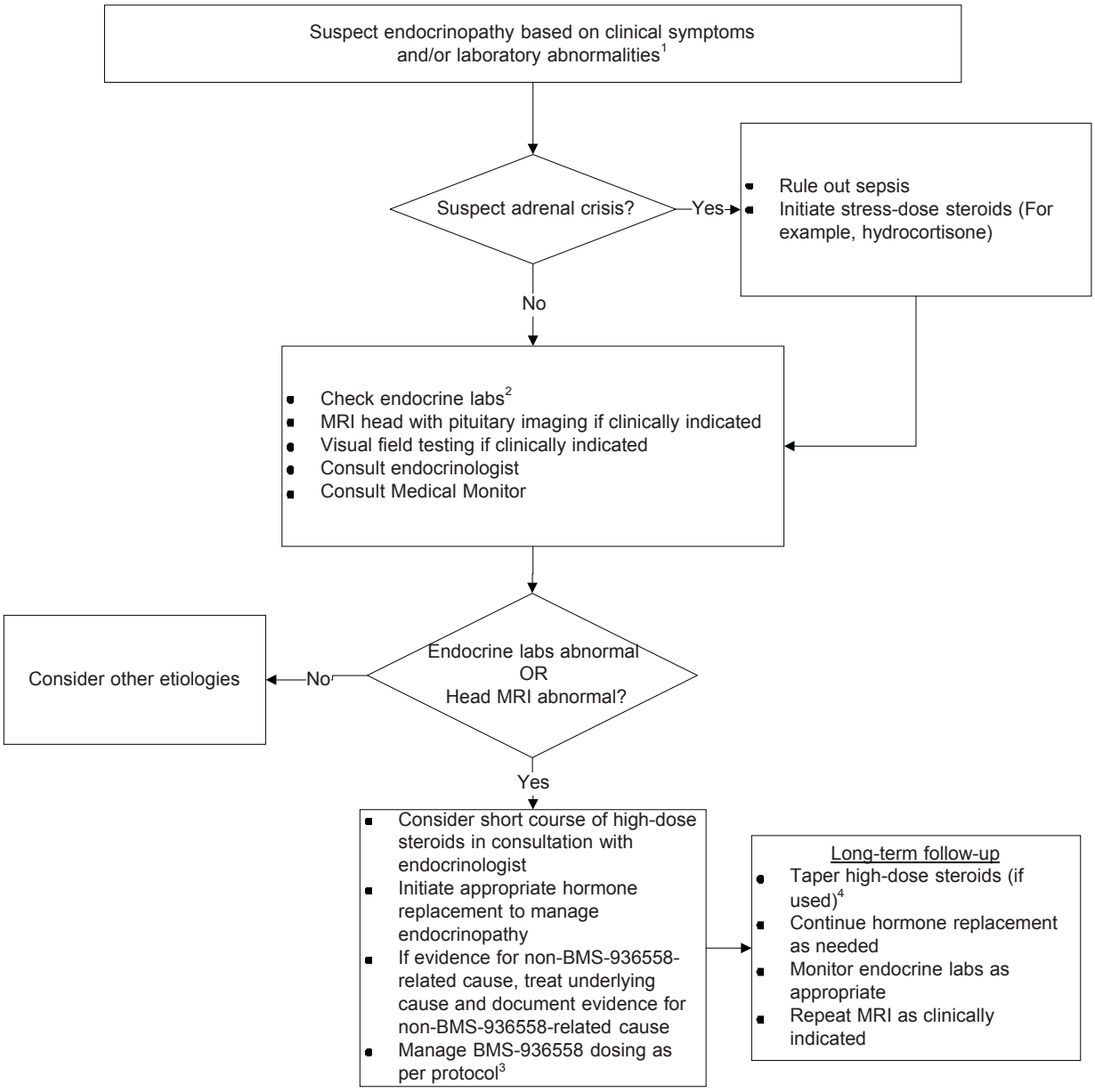
1. Grading as per NC2 CTCAE version 4... 2f both diarrhea and colitis are present, manage as per toxicity with higher grade.
2. 2f infection work-up is positive, do not give steroids, stop following algorithm and treat specific infection.
3. 2f re-treatment with BMS-936558 is allowed as per protocol after completion of steroid taper, consult with Medical Monitor if considering re-treatment.
4. Do not use infliximab if perforation or sepsis is present.



Footnotes:

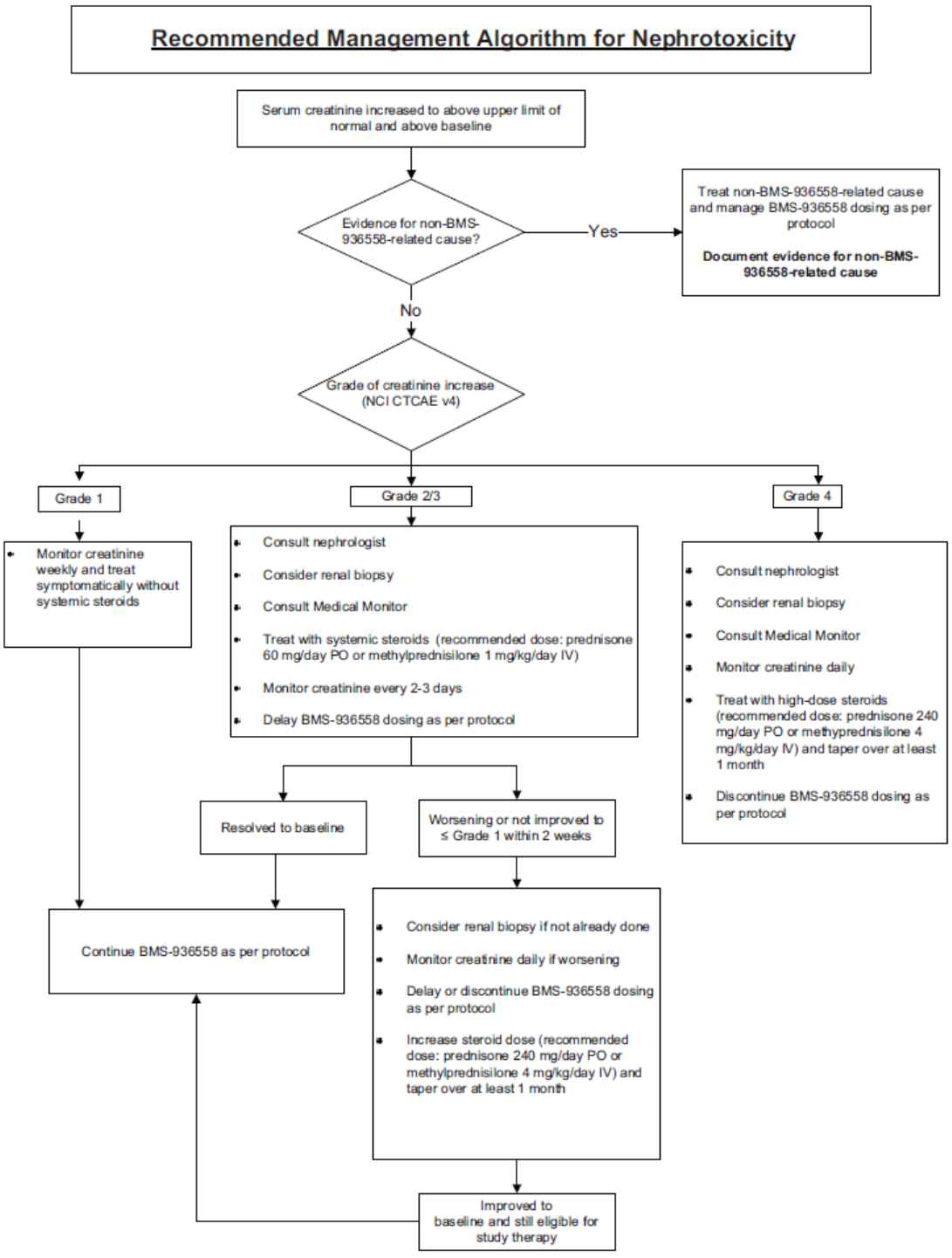
1. If elevations in both AST/ALT and T. Bili are present, the management of BMS-936558 dosing may be different than if only an isolated AST/ALT or T. Bili abnormality is present and may not be dependent on baseline values. Refer to the specific protocol if concurrent elevations occur.
2. Grading as per NCI CTCAE version 4.0

Recommended Management Algorithm for Suspected Endocrinopathy



Footnotes:

1. Cases have typically been identified through routine monitoring of laboratories or as part of a work-up for symptoms such as fatigue.
2. It is important to draw labs at appropriate times; for example, certain labs should be drawn before giving steroids or at specific times of the day.
3. Upon resolution or adequate treatment of endocrinopathy, patients may continue BMS-936558 dosing with appropriate hormone replacement unless limited by protocol.
4. Patients may require chronic steroid replacement to maintain physiologic levels.


Recommended Management Algorithm for Nephrotoxicity
Serum creatinine increased to above upper limit of normal and above baseline
Evidence for non-BMS-936558-related cause?
Yes
Treat non-BMS-936558-related cause and manage BMS-936558 dosing as per protocol
Document evidence for non-BMS-936558-related cause
No
Grade of creatinine increase (NCI CTCAE v4)
Grade 1
Grade 2/3
Grade 4
Monitor creatinine weekly and treat symptomatically without systemic steroids
Consult nephrologist
Consider renal biopsy
Consult Medical Monitor
Treat with systemic steroids (recommended dose: prednisone 60 mg/day PO or methylprednisilone 1 mg/kg/day IV)
Monitor creatinine every 2-3 days
Delay BMS-936558 dosing as per protocol
Consult nephrologist
Consider renal biopsy
Consult Medical Monitor
Monitor creatinine daily
Treat with high-dose steroids (recommended dose: prednisone 240 mg/day PO or methyprednisilone 4 mg/kg/day IV) and taper over at least 1 month
Discontinue BMS-936558 dosing as per protocol
Resolved to baseline
Worsening or not improved to ≤ Grade 1 within 2 weeks
Continue BMS-936558 as per protocol
Consider renal biopsy if not already done
Monitor creatinine daily if worsening
Delay or discontinue BMS-936558 dosing as per protocol
Increase steroid dose (recommended dose: prednisone 240 mg/day PO or methylprednisilone 4 mg/kg/day IV) and taper over at least 1 month
Improved to baseline and still eligible for study therapy

APPENDIX 5 ECOG PERFORMANCE STATUS

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

* Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, and Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655.

APPENDIX 6

Procedure for Obtaining a Urine Protein / Creatinine Ratio

1) Obtain at least 4 ml of a random urine sample (does not have to be a 24 hour urine)
2) Determine protein concentration (mg/dL)
3) Determine creatinine concentration (mg/dL)
4) Divide #2 by #3 above: urine protein / creatinine ratio = protein concentration (mg /dL) / creatinine concentration (mg /dL)

The UPC directly correlates with the amount of protein excreted in the urine per 24 hrs (i.e. a UPC of 1 should be equivalent to 1g protein in a 24hr urine collection)

Protein and creatinine concentrations should be available on standard reports of urinalyses, not dipsticks. If protein and creatinine concentrations are not routinely reported at an Institution, their measurements and reports may need to be requested.

Appendix 7

Moses Lab Protocol
Urine MMPs

Collecting Urine Specimens for MMP Analysis

Obtaining Urine Specimen:

- After obtaining a signed consent form from the participant, obtain a urine specimen in a sterile urine collection cup. At least 2 ml is required for the specimen with 10 to 20 ml the optimum quantity. Ensure the lid is on tightly.

- Using permanent marker, label the urine container with the study number, the participant's unique identifier code and the date of sample collection.

- Immediately after the collection the specimen should be placed on ice and then readily transferred to a minus 20 degree Celsius freezer for storage (-20 °C).

- Samples should be transferred to the Moses Lab on a regular basis. Samples should be transferred in batches or 10 to 20 or if collection is slower, on a monthly basis. Transfer samples on dry ice to ensure they remain frozen.

  The address of the Moses lab is:

  Children's Hospital Boston
  Vascular Biology Program
  Karp Family Research Laboratories, Room 12.214
  1 Blackfan Circle
  Boston, MA 02115-5737
  617-919-2211

- A log should be maintained to record date of sample collection per study participant and when samples are transferred from the site of collection to the Moses lab.

Lab Contacts:

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