THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

Phase II Study of Abraxane Plus Ipilimumab in Patients with Metastatic Melanoma
2011-1157

Core Protocol Information

Short Title	Phase II Study of Abraxane Plus Ipilimimab in Patients with Metastatic Melanoma
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Full Title:	Phase II Study of Abraxane Plus Ipilimumab in Patients with Metastatic Melanoma
Public Description:	The goal of this clinical research study is to learn if the combination of ipilimumab and ABI-007 (abraxane) can help to control metastatic melanoma. The safety of this drug combination will also be studied. Ipilimumab is designed to increase the immune system's ability to fight cancer. Abraxane is designed to stop cancer cells from making new DNA (the genetic material of cells). This may stop the cancer cells from dividing into new cells.
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Which Committee will review this protocol?

(•) The Clinical Research Committee - (CRC)

1.0 Background

The optimum therapy for metastatic melanoma remains unclear. In Western Europe Dacarbazine alone remains the preferred palliative therapy for advanced metastatic melanoma while in the United States, the multi-drug combinations such as CVD (Cisplatin, Vinblastine, Dacarbazine) or Dartmouth Regimen (including Cisplatin, BCNU, Dacarbazine, Tamoxifen) are the most commonly used regimens despite any documented benefit over Dacarbazine in prospectively randomized clinical trials.(1-3) During the past decade several small trials with IL-2-interferon-CVD combination (biochemotherapy) studies suggested improvement in response rate and survival over the results observed with multi-drug chemotherapy combinations. (4-7) To determine the impact of addition of biologicals to combination chemotherapy on response rates and patient survival, 3 prospectively randomized studies Phase III trials were conducted in USA.(8-10) The outcome of these trials failed to show superiority of efficacy of biochemotherapy over combination chemotherapy in terms of response rates and survival. Paclitaxel and Docetaxel have been evaluated for efficacy against metastatic melanoma. The response rates to these drugs ranged between 13 to 15 % in Chemonaive patients. Phase II study of ABI-007 in patients with metastatic melanoma gave a response rate 20% in similar patient population indicating that it may be the most effective taxane against metastatic melanoma.

Multiple Phase II clinical trials with Ipilimumab alone, Ipilimumab in combination with DTIC or immunotherapeutic agents such as interferon, IL-2 or gp-100 gave durable complete responses similar to IL-2. (12-16) We have been evaluating Ipilimumab – temozolomide combination in patients with metastatic melanoma without prior chemotherapy over the past several years. The combination is well tolerated and the toxicity profile is similar to Ipilimumab -Dacarbazine combination that was evaluated in chemonaive patients earlier.(16) Clinical trials during the past 8 years showed that Ipilimumab containing regimens gives durable responses like IL-2.(17)

ABI-007 is a novel Cremophor EL-free, non-crystalline, amorphous, albumin-bound particle form of paclitaxel suspended in normal saline with several advantages over Taxol:
Preclinical models consistently demonstrated improved tolerability, increased antitumor activity and higher intratumor paclitaxel levels for ABI-007 compared to Taxol. Recent mechanistic studies indicate that this increased antitumor activity may be due to increased tumor uptake of paclitaxel that is mediated through albumin-receptors on tumor neovasculature. ABI-007 is Cremophor EL-free and therefore associated with a reduced risk of hypersensitivity and no requirements for premedication as compared to Taxol.
ABI-007 does not require steroid co-medication. ABI-007 is better tolerated than Taxol. In a Phase I trial using an every 3 week schedule of administration, the maximum tolerated dose of ABI-007 (300 mg/m2) was substantially higher than the labeled dose for Taxol (175 mg/m2).
The antitumor tumor activity of ABI-007 given every 3 weeks was greater than that observed with Taxol in women with metastatic breast cancer.

Rationale

There is compelling evidence that chemotherapy-induced tumor cell death triggers an innate immune response, which is required for maximal therapeutic benefit. Dying tumor cells are recognized by Toll-like receptor 4 (TLR4) on dendritic cells, which leads to a widespread anti-tumor immune response. (21) The Toll-like receptors are a large family of pattern-recognition receptors used by cells of the innate immune system to respond to specific lipid, protein, and nucleic acid components produced by pathogens. (22) There is mounting evidence that innate immunity is also involved in recognizing and destroying tumor cells. Apetoh and colleagues showed that tumor cells killed by chemotherapeutic agents release HMGB1 (high-mobility group B1), an abundant DNA-binding nuclear protein that serves as a "danger signal" for the immune system. (22) Once released, HMGB1 bind TLR4 and stimulate dendritic cells to secrete pro-inflammatory cytokines and activate an innate immune response. Stimulation of complementary immune pathways has been shown to be highly effective in eradicating large established tumors. (23, 24) An acute release of de novo tumor antigen from apoptosis induced by anti-DR5 antibody followed by boosting the T-cell activation phase using anti-CD40 and anti-41BB antibodies is possible (23) Another study, with similar results, used the same synergistic treatment combination, except that activation of invariant NKT cells with alfa-galactosylceramide was used in place of anti-CD40 (23) Our clinical trial protocol here will put into practice a similar synergistic approach through immunotherapy with interferon-alfa, interleukin-2 and anti-CTLA4 therapy. IPI-Biotherapy will lead to intense cytokine release and stimulation of cellular immunity.

The taxanes paclitaxel and docetaxel have shown response rates in the range of 10 to 15% in a number of reported studies.(25) Dr. Evan Hersh conducted a Phase II trial of ABI-007 in patients with previously treated and chemotherapy naive malignant melanoma.(26) Treatment was given weekly for 3 weeks followed by a one-week break period. The objective response rate was 22% in chemotherapy naive patients. The higher ABI-007 dose administered to chemotherapy naïve patients, while resulting in a higher incidence of peripheral neuropathy, was otherwise generally well-tolerated. Myelosuppression was not problematic in either cohort. (Hersh et al Cancer 2010; 116:155-63).

Clinical trials involving the use of chemotherapy, interferon, interleukin-2 or anti-CTLA-4 drugs, administered separately have failed to give clinically significant anti-tumor T-cell responses. Thus, there is a strong rationale for combining immunologic agents, with cytotoxic anticancer agent in a novel chemoimmunotherapy. Our proposed novel therapy is designed in a rational fashion combining ABI-007 with Ipilimumab together to induce tumor destruction that acutely releases tumor antigen into the system for T-cell activation by antigen-presenting cells (APC), and then cause T-cell activation and expansion against these newly-released antigens (and pre-existing antigens) to generate highest possible number of tumor antigen-specific T cells necessary for complete destruction of the tumor cells. This will improve the anti-tumor immunity and survival. Immunologic

evaluation of the patients will be performed prior to start of therapy and during the therapy to clearly define the immune response and correlate it with clinical response.

2.0 Background Drug Information

2.1 ABI-007: Paclitaxel Protein-bound Particles

2.2.1 The Product

ABI-007 (paclitaxel protein-bound particles for injectable suspension)(albumin-bound) is a Cremophor EL-free, albumin-bound particle form of paclitaxel. Each 50 mL vial contains 100 mg of paclitaxel, and approximately 900 mg of human albumin, as a white to yellow sterile lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection.

2.2.2 Introduction

ABI-007 is a unique protein formulation of a non-crystalline, amorphous form of paclitaxel in an insoluble particle state. ABI-007 has been developed to reduce the toxicities associated with Taxol (paclitaxel) Injection (in which paclitaxel - from the native crystalline form - is in solution with Cremophor EL/ethanol as the solvent) while maintaining or improving its chemotherapeutic effect. ABI-007 has been approved in over 35 countries to date, including the U.S. and Canada (and is under review in a number of other countries) for the treatment of women with metastatic breast cancer.

2.2.3 Preclinical Studies with ABI-007

Preclinical studies comparing ABI-007 to Taxol demonstrated lower toxicities, with a MTD approximately 50% higher for ABI-007 compared to Taxol. At equal doses there was less myelosuppression and improved efficacy in a xenograft tumor model of human mammary adenocarcinoma. At equitoxic doses of paclitaxel, ABI-007 was found to be markedly more efficacious in these animal models than Taxol.20

2.1.4 Clinical Studies with ABI-007

2.1.4.1 Every 3 Weeks Schedule

In a Phase I study, the maximum tolerated dose (MTD) of ABI-007 was determined to be 300 mg/m2 by 30 minute infusion every 3 weeks, without premedication or G-CSF support. Two multicenter Phase II studies have evaluated 2 dose levels of ABI-007 (300 mg/m2, n=63, and 175 mg/m2, n=43) in patients with metastatic breast cancer. The response rates (complete response [CR]+partial response [PR]) in these 2 Phase II trials were 40% (95% CI 25-54%) for the 175 mg/m2 dose, and 48% (95% CI 35-60%) for the 300 mg/m2 dose. Of 39 patients receiving 300 mg/m2 as first-line therapy for metastatic breast cancer, 64% (95% CI 49-79%) responded (CR+PR). This was contrasted with a 45% response rate in similar patients at the lower dose level. Grade 4 neutropenia was noted in 24% of patients at the higher dose level, occurred primarily during the first cycle and resolved rapidly. A Phase III trial in patients with metastatic breast cancer compared ABI-007 260 mg/m2 to Taxol 175 mg/m2 given every 3 weeks. Significantly higher efficacy for ABI-007 vs Taxol was demonstrated as measured by response rates (CR+PR, 33% vs 19%, $p<0.001$), time to tumor progression (23.0 vs 16.6 weeks, $p=0.002$), and progression-free survival (22.7 vs 16.6 weeks, $p=0.003$). Survival was longer with ABI-007, although the difference was not statistically significant (65.0 vs. 55.3 weeks, $p=0.322$).

2.1.4.2 Weekly for 3 Weeks, Every 4 Weeks Schedule

A Phase I study of ABI-007 administered weekly for 3 weeks followed by a 1 week rest in patients with advanced solid tumors has recently been completed.21 The MTDs for heavily and lightly pre-treated patients were 100 and 150 mg/m2 respectively. Dose limiting toxicities included myelosuppression and peripheral neuropathy. Premedication was not required, and unexpected, non-taxane associated toxicities were not observed. In a Phase II trial in heavily pretreated patients with taxane-refractory metastatic breast cancer, objective antitumor responses occurred in 18% of women treated with ABI-007 100 mg/m2 on this schedule.22 Toxicity was minimal and this study has been amended to evaluate an increased dose of 125 mg/m2 in this patient population. The tolerability of 150 mg/m2 in previously untreated patients has been confirmed in an interim analysis of 32 patients with malignant melanoma who received a mean of 3.5 cycles (range 1-9). To date there has been 1 case of Grade 3 sensory neuropathy (no Grade 4) and 1 case of Grade 4 neutropenia.

2.2.5 ABI-007 in Metastatic Malignant Melanoma

The taxanes paclitaxel and docetaxel have shown response rates in the range of 10 to 15% in a number of reported studies.23,24 Dr. Evan Hersh conducted a Phase II trial of ABI-007 in patients with previously treated and chemotherapy naive malignant melanoma. Treatment was given weekly for 3 weeks followed by a one-week break period. A higher weekly dose of ABI-007 was given to chemotherapy naive patients (150 mg/m2). Results from the trial are presented in the table below. As expected, the objective response rate was higher in chemotherapy naive patients. The higher ABI-007 dose administered to chemotherapy naive patients, while resulting in a higher incidence of peripheral neuropathy, was otherwise generally well-tolerated. Myelosuppression was not problematic in either cohort. (Hersh et al Cancer 2010; 116:155-63).

Parameter	Previously treated	Chemotherapy naive
Total patients studied	37	37
ABI-007 Dose d 1, 8, 15 q 28 days	100 mg/m^2	150 mg/m^2
Mean delivered dose intensity (mg/m^2/wk)	75	96
Patients requiring dose reduction	22%	51%
Objective Response Rate	3%	22%
Stable Disease ≥ 16 weeks (excluding objective responders)	35%	27%
Disease Control	38%	49%
Progression Free Survival (months, 95% CI)	3.5 (1.7, 5.6)	4.5 (3.4, 6.7)
Survival (months, 95% CI)	12.1 (6.5, 17.5)	9.6 (6.7, 23.7)
Peripheral Neuropathy (worst grade on study)		
Grade 1	32%	27%
Grade 2	24%	32%
Grade 3	5%	16%
Grade 4	0%	3%
Neutropenia Grade 4 (any time on study)	3%	5%
Thrombocytopenia Grade 2, 3 or 4 (any time on study)	3%	0%

2.2.6 Potential Risks of ABI-007

ABI-007 is not formulated in Cremophor and thus the risk of hypersensitivity reactions is much less than that of Taxol. The major risks of ABI-007 were known toxicities of paclitaxel. See the Investigator Brochure for a complete description of all toxicities reported.

Myelosuppression, predominantly neutropenia. Grade 4 neutropenia typically resolved in < 7 days and did not require colony stimulating factor support.

Peripheral neuropathy, predominantly sensory. Grade 3 peripheral neuropathy typically improved to Grade 1 or 2 within 21 days of holding the ABI-007 dose at which time therapy could be restarted at a lower dose.

Nausea and vomiting. Nausea and vomiting were typically Grade 1 or 2 and responded to standard anti-emetic regimens.

Myalgias and arthralgias. Myalgias and arthralgias were typically Grade 1 or 2 and responsive to standard acetaminophen-containing medication.

Mucositis. Mucositis was typically Grade 1 or 2 and not dose limiting.

Alopecia. Similar to that seen with Taxol.

2.2.7 Advantages of ABI-007

ABI-007 is a novel Cremophor EL-free, non-crystalline, amorphous, albumin-bound particle form of paclitaxel suspended in normal saline with several advantages over Taxol:

- Preclinical models consistently demonstrated improved tolerability, increased antitumor activity and higher intratumor paclitaxel levels for ABI-007 compared to Taxol. Recent mechanistic studies indicate that this increased antitumor activity may be due to increased tumor uptake of paclitaxel that is mediated through albumin-receptors on tumor neovasculature.26
- ABI-007 does not require steroid co-medication.
- ABI-007 is better tolerated than Taxol. In a Phase I trial using an every 3 week schedule of administration, the maximum tolerated dose of ABI-007 (300 mg/m2) was substantially higher than the labeled dose for Taxol (175 mg/m2).27
- The antitumor tumor activity of ABI-007 given every 3 weeks was greater than that observed with Taxol. In Phase II trials, antitumor activity was documented in metastatic breast cancer and a Phase III study utilizing ABI-007 at a dose of 260 mg/m2 every 3 weeks demonstrated increased objective response rates and time to tumor progression compared to standard doses of Taxol in women with metastatic breast cancer.
- The major components of ABI-007 are unmodified paclitaxel and human albumin. The absence of Cremophor EL in the formulation allows the infusion of ABI-007 in approximately 30 minutes.
- ABI-007 is Cremophor EL-free and therefore associated with a reduced risk of hypersensitivity and no requirements for premedication as compared to Taxol. The Cremophor EL constituent in Taxol requires special non-DEHP tubing and in-line filters for intravenous administration, since Cremophor EL causes leaching of the tubing plasticizers. ABI-007 requires no special tubing or in-line filters.

2.2.8 Packaging, Labeling, and Storage of Study Drug

ABI-007 will be supplied by the Celgene in single-use vials. Each single-use 50 mL vial will contain paclitaxel (100 mg) and approximately 900 mg human albumin (HA) as a stabilizer. Each vial will be labeled according to country-specific regulatory requirements for labeling of investigational products. Unreconstituted ABI-007 should be stored at controlled room temperature (25°C or 77°F; excursions permitted to 15-30ºC [See USP controlled room temperature]). Reconstituted ABI-007 should be used immediately. If not used immediately, the vial of reconstituted ABI-007 must be placed in its carton and be placed in a refrigerator at 2° to 8°C (36° to 46°F) for a maximum of 8 hours. Both forms should be stored in an area free of environmental extremes and must be accessible only to study personnel. Temperature records for ABI-007 must be made available to Celgene or other sponsor nominated Contract Research Organization (CRO) monitoring teams for verification of proper study drug storage. Only completely unused study drug vials should be destroyed per institutional policy. Partially used and completely used vials should be destroyed according to the site's guidelines, and their disposition should be recorded on the Investigational Drug Accountability Record Form. The

investigator, or designee, shall record the dispensing of study drug to patients and any remaining study drug after dosing in a study drug accountability record. The study drug record will be made available to Celgene, or other authorized Celgene-designated monitoring personnel for the purpose of accounting for the study drug supply. Inspections of the study drug supply for inventory purposes and assurance of proper storage will be conducted as necessary. Any significant discrepancy will be recorded and reported to Celgene or their designee and a plan for resolution will be documented.

2.2.9 Study Medication Administration

NOTE: The use of an in-line filter is not recommended.

ABI-007 will be reconstituted by appropriate study personnel and administered to the patient in the study site. The investigator will calculate the body surface area (BSA) of the patient using methods that are standard for their institution in order to determine the total amount of paclitaxel to be administered.

Reconstitution and use of ABI-007:

1. Calculate the patient's BSA according to standard institutional methods. BSA will be calculated at Baseline and can be recalculated according to institutional standards. BSA must be recalculated if body weight changes by more than 10%. Dosing BSA may be capped if the treating physician believes it is in the best interest of an obese patient.
2. Calculate the total dose (in mg) to be administered by: Total Dose (mg) = BSA x (study dose mg/m2)
3. Calculate the total number of vials required by: Total Number of Vials = Total Dose (mg) 100 (mg/vial) Round up the number of vials to be reconstituted to the next higher whole number when a fractional number of vials is obtained by the above formula (eg, if the total number of vials = 4.05 or 4.5, then 5 vials would be reconstituted).
4. Using sterile technique, prepare the vials for reconstitution.
5. Swab the rubber stoppers with alcohol.
6. Reconstitute each ABI-007 vial by using a 50 or 60 cc sterile syringe to inject 20 mL of 0.9% Sodium Chloride Injection or equivalent into each vial over a period of not less than 1 minute (Note: Change the syringes after reconstituting every 3 vials).
   - Slowly inject the 20 mL of 0.9% Sodium Chloride Injection over a minimum of 1 minute, using the sterile syringe directing the solution flow onto the inside wall of the vial.
   - DO NOT INJECT the 0.9% Sodium Chloride Injection solution directly onto the lyophilized cake as this will result in foaming.
   - Once the injection is complete, allow the vial to sit for a minimum of 5 minutes to ensure proper wetting of the lyophilized cake/powder.
   - Gently swirl and/or invert the vial slowly for at least 2 minutes until complete dissolution of any cake/powder occurs. Avoid generation of foam.
   - If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides. Each mL of reconstituted product will contain 5 mg of paclitaxel.
7. Calculate the exact total dosing volume of 5 mg/mL suspension required for the patient: Dosing volume (mL) = Total dose (mg) / 5 (mg/mL)
8. The reconstituted sample should be milky and homogeneous without visible particulates. If unsuspended powder is visible, the vial should be gently inverted again to ensure complete resuspension, prior to use.
9. Use immediately following reconstitution. If not used immediately, replace the reconstituted vial in the carton and store reconstituted ABI-007 in a refrigerator for not more than 8 hours.
10. Using a new, sterile 50 or 60 cc syringe, withdraw the reconstituted ABI-007 solution. Do not remove the rubber stopper from the ABI-007 vials as this can compromise the sterility of the drug preparation.
11. Inject the calculated dosing volume of reconstituted ABI-007 suspension into an empty sterile, standard PVC IV bag, using an injection port. Inject perpendicularly into the center of the injection port to avoid dislodging plastic material into the IV bag. Repeat steps 9 and 10 until the patient's entire required dose is injected into the IV bag.
12. Remove the injection port.
13. Once the exact volume of reconstituted ABI-007 has been withdrawn from the vials, discard any excess solution left over in accordance with standard operating procedures for cytotoxic drugs.
14. Administer the calculated dosing volume of reconstituted ABI-007 suspension by IV infusion over 30 minutes to 40 minutes. The use of an in-line filter is not recommended.

2.2.10 Receipt and Return of Study Drug

Upon receipt of the study drug supplies, the investigator or designee will conduct an inventory and sign the study drug receipt. A copy of the drug receipt should be made and retained in the investigator's regulatory file records. The original should be sent to the address indicated on the stamped self addressed envelope included with the shipment.

A representative from Celgene or his/her designee will inspect the study drug inventory, and will authorize the destruction of any remaining unused study drug. If the investigational site has a policy, procedure or SOP detailing the process to follow for study drug destruction, the pharmacist or designee can choose to destroy the study drug on site. The following information must be recorded on the site's pharmacy drug accountability log: quantity of vials destroyed, expiration date and lot number. The pharmacist must document that the study drug was destroyed in accordance with their institution's drug destruction policy or SOP. A drug destruction memo and the site's drug destruction SOP/policy should be sent to Celgene Medical Operations Dept. A copy of the drug destruction memo should be retained at the clinical site. In the event of study completion or termination, a copy of all pharmacy records (drug dispensing log, drug accountability log and any destruction memos) must be mailed to Celgene Medical Operations.

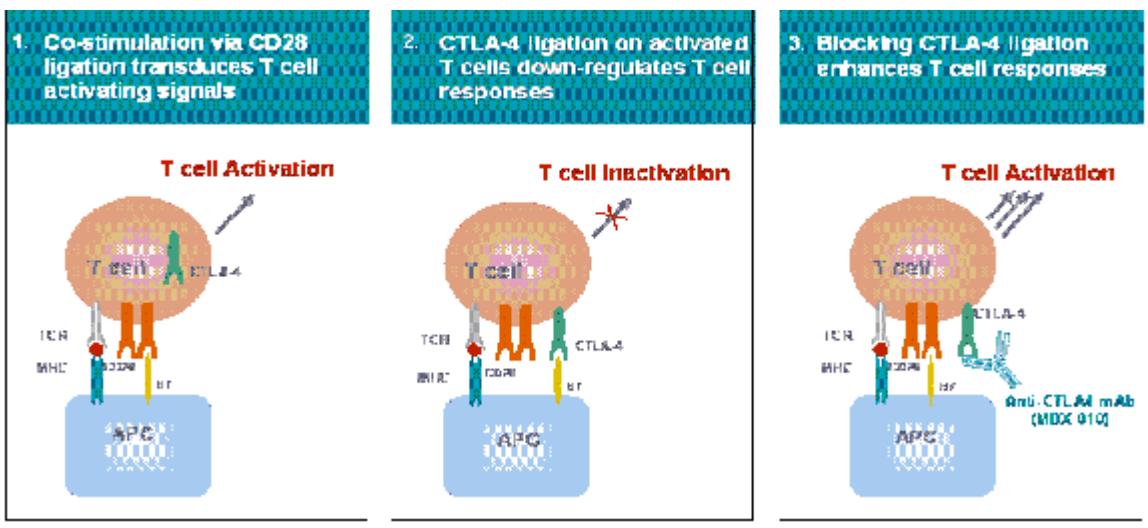
2.1 Ipilimumab

CTLA-4 and T Cell Activation

Advances in the understanding of 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 stimulation is mediated by engagement of CD28 on the T cell surface by members of the B7 family on the

antigen-presenting cell (APC). [Lenschow D.J., et al., CD28/B7 system of T cell costimulation. Ann Rev Immunol, 1996. 14: p. 233-58]. (See Figure 1.)

Figure 1 Mechanism of Action



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 [Schwartz R.H. Costimulation of T lymphocytes: the role of CD28, CTLA4, and B7/BB1 in interleukin-2 production and immunotherapy. Cell, 1992. 71(7): p. 1065-8]. The fact that tumor cells do not express B7 contributes to their poor capacity to elicit immune responses [Chen L.S., et al., Costimulation of antitumor immunity by the B7 counterreceptor for the T lymphocyte molecules CD28 and CTLA-4. Cell, 1992. 71(7): p. 1093-102., Townsend S.E., et al., Tumor rejection after direct costimulation of CD8+ T cells by B7-transfected melanoma cells. Science, 1993. 259(5093): p. 368-70].

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 [Townsend S.E., et al., Specificity and longevity of antitumor immune responses induced by B7-transfected tumors. Cancer Res, 1994. 54(24): p.6477-83., Allison J.P., et al., Manipulation of co-stimulatory signals to enhance antitumor t cell responses. Curr Opin Immunol, 1995. 7(5): p. 682-6].

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 [Linsley P.S., et al., CTLA-4 is a second receptor for the B cell activation antigen B7. J Exp Med, 1991. 174(3): p. 561-9]. 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 [Thompson C.B., and Allison J.P. The emerging role of CTLA-4 as an immune attenuator. Immunity, 1997. 7(4): p.445-50]. 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 [Walunas T.L., et al., CTLA-4 can function as a negative regulator of T cell activation. Immunity, 1994. 1(5): p. 405-13., Kearney E.R., et al., Antigen-dependent clonal expansion of a trace population of antigen-specific CD4+ T cells in vivo is dependent on CD28 costimulation and inhibited by CTLA-4. J Immunol, 1995. 155(3): p. 1032-6., Krummel M.F. and Allison J.P. CD28 and CTLA-4 have opposing effects on the response of T cells to stimulation. J Exp Med 1995; 182(2): p. 459-65., Krummel M.F., et al., Superantigen responses and co-stimulation: CD28 and CTLA-4 have opposing effects on T cell expansion in vitro and in vivo. Int Immunol, 1996. 8(4): p. 519-23]. Blocking CTLA-4-B7 interaction while preserving signaling via CD28 resulted in enhanced T cell responses in vitro.10

Perhaps the most convincing demonstration of the down-regulatory role of CTLA-4 came from examination of mice with a null mutation [Tivol E.A., et al., Loss of CTLA-4 leads to massive lymphoproliferation and fatal multiorgan tissue destruction, revealing a critical negative regulatory role of CTLA-4. Immunity, 1995. 3(5): p. 541-7., Waterhouse P. et al., Lymphoproliferative disorders with early lethality in mice deficient in CTLA-4. Science, 1995. 270(5238): p. 985-8., Chambers C.A., et al., Lymphoproliferation in CTLA-4-deficient mice is mediated by costimulation-dependent activation of CD4+ T cells. Immunity, 1997, 7(6): p. 885-95]. 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.12

2.1.1 Pharmacology of Ipilimumab

Ipilimumab is a human immunoglobulin G (IgG1)ê 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.

2.1.2 Pre-Clinical Toxicology of Ipilimumab

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

The *in vitro* studies demonstrated that Ipilimumab did not mediate CDCC of PHA- or (CD)3-activated human T cells. However, low to moderate ADCC activity was noted at concentrations up to 50 ug/mL. These data are consistent with the requirement of high levels of antigen expression on the surface of target cells for efficient ADCC or CDCC. Since Ipilimumab is a human IgG1, an isotype generally capable of mediating CDCC and ADCC, the lack of these activities is likely due to a very low expression of CTLA-4 on activated T cells. Therefore, these data suggest that Ipilimumab treatment would not result in depletion of activated T cells *in vivo*. Indeed, no depletion of T cells or T cell subsets were noted in toxicology studies in cynomolgus monkeys.

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

2.1.3 Human Pharmacokinetics of Ipilimumab

Pharmacokinetic (PK) profiles for Ipilimumab have been analyzed. The primary objective of Protocol MDX010-015 was to determine the safety and PK profile of single and multiple doses of Ipilimumab derived from a transfectoma or hybridoma cell line. Mean plasma concentrations of Ipilimumab administered at doses of 3 mg/kg (hybridoma-derived drug product); 2.8 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, and 20 mg/kg (transfectoma-derived drug product) demonstrated approximate dose proportionality. Equimolar doses of hybridoma-derived and transfectoma-derived drug product had comparable PK profiles. The range of mean volume of distribution at steady state (Vss) across cohorts 2.8, 3, 5, 7.5, 10, 15, and 20 mg/kg, was 57.3 to 82.6 mL/kg, indicating drug distribution was mostly limited to the intravascular space. The clearance was low (range 0.11 to 0.29 mL/h/kg) and reflective of the half-life (range 297 to 414 h), which is consistent with the long terminal disposition phase of Ipilimumab. There was moderate variability in the PK parameters among subjects, with CV of 11% to 48% in AUC(0-21d), 20% to 59% in CL, and 17% to 46% in Vss.

2.1.4 Clinical Safety with Ipilimumab

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

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

2.1.4.1 Details of Drug-Related Adverse Events

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

2.1.4.2 Drug-Related Serious Adverse Events

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

Among subjects treated with Ipilimumab 10 mg/kg, SAEs considered possibly, probably, or definitely related to study drug were reported for 26% of subjects (176/675). Drug related SAEs reported in at least 1% of the 675 subjects at 10 mg/kg included diarrhea (10%), colitis (7%), vomiting (3%), dehydration (3%), autoimmune hepatitis (2%), hypopituitarism (2%), nausea (2%),

abdominal pain (2%), pyrexia (2%), aspartate aminotransferase increased (1%), alanine aminotransferase increased (1%), and fatigue (1%).

2.1.5 Immune-Related Adverse Events (irAEs) with Ipilimumab

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

Approximately 60% of subjects developed any grade irAEs which involved predominately the gastrointestinal (GI) tract, endocrine glands, liver, or skin. Based on data from the safety database, the number of subjects with serious, dose-limiting irAEs was approximately 15% (401/2633), including 8.2% for serious GI irAEs (diarrhea and/or colitis), 2.2% of serious endocrinopathy (primarily hypophysitis/hypopituitarism) 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.

2.1.5.1 Drug-Related Deaths

Based on reports from the safety data base as of June 30, 2008, there have been reports of death (approximately 1% [28/3000]), deemed by the investigator as possibly related to the administration of study drug. The most common cause of drug related deaths was GI perforation. Other causes included multiorgan failure, sepsis, hypotension, acidosis, and adult respiratory distress syndrome. For details on all drug-related deaths, refer to the current version of the Ipilimumab Investigator Brochure.

2.1.5.2 Safety of 10 mg/kg Multiple Doses

Based on a review of the program-wide SAE data as previously reported, evidence had suggested that Ipilimumab-associated irAEs were dose dependent in frequency, and higher irAE rates had been observed at 10 mg/kg than at lower doses of Ipilimumab. Subsequently, this dose-dependent effect was further demonstrated in CA184-022 in which three dose levels of Ipilimumab were studied, including 0.3 vs 3 vs 10 mg/kg. Table 1 summarizes the overall irAE frequencies by dose from CA184-022 based on safety data from the locked clinical database.

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

Table 1.Summary of Immune-Related AEs by Treatment Groups - Treated Subjects (CA184-022)

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

2.1.5.3 Neuropathies

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

2.1.6 Clinical Efficacy of Ipilimumab

Treatment with Ipilimumab has demonstrated clinically important and durable tumor responses in several malignancies including melanoma, prostate cancer, and renal cell carcinoma. The most extensively studied tumor type has been malignant melanoma. Based on preliminary results, Ipilimumab is active in patients with advanced stage malignant melanoma. The objective responses observed with Ipilimumab may be considered durable as they have occurred across a spectrum of doses and schedules.

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

2.1.6.1 Relationship Between Response and Immune Breakthrough Events in Patients with Metastatic Melanoma

Drug-related AEs of any grade considered to be immune-mediated in nature (irAEs) were reported for 54.0% of subjects in clinical studies of Ipilimumab. These irAEs are a consequence of inhibiting CTLA-4 function and most were reported as Grade 1 or 2. An association between BORR and higher grade (Grade 3-4) irAEs was suggested in early studies of Ipilimumab 3 mg/kg but this association was not observed in 4 Phase 2 studies of Ipilimumab (CA184022, CA184008, CA184007 and CA184004). There were proportionally more subjects with irAEs of any grade who experienced response or stable disease than subjects without irAEs who experienced response or stable disease, but due to the small sample sizes, these observations were statistically inconclusive (CA184022 Clinical Study Report. A Randomized, Double-Blind, Multi-center, Phase II Fixed Dose Study of Multiple Doses of Ipilimumab (Ipilimumab) Monotherapy in Patients with Previously Treated Unresectable Stage III or IV Melanoma. Bristol-Myers Squibb Company and Medarex Inc, 2008. Document Control No. 930026869., CA184008 Clinical Study Report. A Multicenter, Single Arm Phase 2 Study of Ipilimumab (BMS 734016) Monotherapy in Patients with Previously Treated Unresectable Stage III or IV Melanoma. Bristol-Myers Squibb Company and Medarex Inc, 2008. Document Control No. 930025464., CA184007 Clinical Study Report. Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study Comparing the Safety of Ipilimumab Administered With or Without Prophylactic Oral Budesonide (Entocort EC) in Patients with Unresectable Stage III or IV Malignant Melanoma. Bristol-Myers Squibb Company and Medarex Inc, 2008. Document Control No. 930026874).

2.1.7 Overall Risk/Benefit Assessment

Results from the 3 primary efficacy studies of Ipilimumab suggest that the 10 mg/kg dose is active and offers the best benefit to risk ratio based on a 27.1% to 35.1% rate of disease control and a favorable 1-year survival rate of 48.6% to 59.1% compared with that reported in the literature (25.5% to 35%). (Korn EL, Liu P-Y, Lee S, et al. Meta-analysis of phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmarks for future phase II trials. J Clin Oncol. 2008;26:527-534., Chapman PB, Einhorn E, Meyers ML, Saxman S, Destro AN, Panageas KS, Begg CB, et al. Phase III Multicenter Randomized Trial of the Dartmouth Regimen Versus Dacarbazine in Patients with Metastatic Melanoma. J Clin Oncol. 1999;17(9)2745-2751., Middleton MR, Grob JJ, Aaronson N, Fierlbeck G, Tilgen W, Seiter S, Gore M, et al. Randomized Phase III Study of Temozolomide Versus Dacarbazine in the Treatment of Patients With Advanced Metastatic Malignant Melanoma. J Clin Oncol. 2000;18:158-166., Bedikian AY, Millward, M, Pehamberger H, Conry R, Gore M, Trefzer U, Pavlick AC, et al. Bcl-2 Antisense (oblimersen sodium) Plus Dacarbazine in Patients With Advanced Melanoma: the Olimersen Melanoma Study. J Clin Oncol. 2006:24:4738 4745). Substantial reductions in total tumor burden, including widely disseminated disease in the skin, lung, and/or other visceral disease sites, were reported. More than half the responses were reported in subjects staged with M1b or M1c advanced melanoma disease, which is most resistant to approved therapies. The kinetics of Ipilimumab resulted in known patterns of clinical activity (CR, PR and SD) as well as novel patterns, characterized by reductions in total tumor burden, including existing and new lesions, after initial tumor volume increase and/or after appearance of new lesions. In the pretreated population at 10 mg/kg in 2 of the 3 studies, disease control after initial tumor volume increase and/or new lesions was reported for 9.7% of subjects. Across all 3 studies, stable disease was often accompanied by clinically relevant reductions in tumor burden compared to baseline. All patterns of response, including SD, appeared to result in favorable survival, based on 1-year survival rates.

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

Treatment with Ipilimumab resulted in clinical activity in pretreated and previously untreated subjects with advanced melanoma. Clinically relevant reductions in the tumor burden from baseline were reported, together with a preliminary evidence of improved overall survival compared with published survival rates. These findings, together with evidence of a safety profile that is manageable with careful monitoring and appropriate intervention for treatment of immune-related toxicities, suggest an acceptable benefit to risk ratio. The overall risk-benefit ratio for patients entering this protocol is therefore at least comparable to and possibly better than alternative options.

3.0 Objectives

Primary Objective:

1. To determine if the combination of ABI-007-Ipilimumab combination can delay disease progression in patients with metastatic melanoma.

2. To determine the rate of progression-free survival (PFS) at 6 months of the ABI-007-Ipilimumab combination.

Secondary Objectives:

1. To determine the efficacy of ABI-007-Ipilimumab combination as measured by complete and partial response rate, response duration, and overall survival in patients with metastatic unresectable stage III/IV melanoma.
2. To determine the safety of IV ABI-007-Ipilimumab combination, given IV for the treatment of patients with metastatic melanoma
3. To study the immunologic changes in patients who receive this therapy.

4.0 Patient Eligibility

4.1 Inclusion criteria:

1. Patients with histologically documented diagnosis of advanced stage IV or unresectable stage III mucosal or cutaneous melanoma are eligible.
2. They must have recurrent melanoma with measurable or evaluable sites of disease, 1.0 cm or larger, in order to assess the response to treatment by the immune-related response criteria (irRC).
3. Patients should not have been previously treated with cytotoxic drugs and immunotherapeutic agents for unresectable Stage III or Stage IV disease. Prior Ipilimumab in metastatic setting is not allowed. Prior therapy may include one line of targeted therapy for metastatic disease ie BRAF or MEK inhibitor. At least 3 weeks should have passed since the last dose of prior adjuvant interferon therapy and prior targeted therapies, and all previous therapy related toxicities should have resolved before starting study treatment. Prior adjuvant interferon is permitted. Prior cytotoxic therapy in adjuvant or metastatic setting is not allowed. Prior Ipilimumab in adjuvant setting is not allowed. Prior adjuvant therapy with targeted therapy including but not limited to B-RAF, MEK inhibitors etc. is allowed. Prior palliative radiation therapy for metastatic melanoma is permitted provided the patient has unirradiated metastatic sites for response evaluation and has fully recovered from its toxicity.
4. Patients between 12 years of age and 70 years of age with an ECOG performance status of 0 or 1 will be eligible
5. They should have normal blood counts with a WBC count of more than or equal to 3000/mm^3 an absolute neutrophil count of more than or equal to 1500/mm^3 and a platelet count of more than 100,000/mm^3, Hemoglobin > 9.0 g/dL and have no impairment of renal function (serum creatinine less than 1.1 mg/dl for females and less than 1.4 mg/dl for males), hepatic function (serum bilirubin level of less than 1.5 mg/dl, AST and ALT ≤ 2.5X ULN ***unless presence of hepatic metastasis sin which case AST and ALT ≤ 5X ULN are acceptable.*** Alk Phos ≤ 2.5X ULN) and no evidence of significant cardiac or pulmonary dysfunction.
6. They should have no significant intercurrent illness such as an active infection associated with fever lasting more than 24 hours requiring antibiotics, uncontrolled psychiatric illness, hypercalcemia (calcium greater than 11 mg), or active GI bleeding.

Females of child-bearing potential (non-childbearing is defined as greater than one year post-menopausal or surgically sterilized) must use acceptable contraceptive methods(abstinence, intrauterine device, oral contraceptive or double barrier devices) and must have a negative serum or urine pregnancy test within 72 hours prior to beginning treatment on this trial. Sexually active men must also use acceptable contraceptive methods for the duration of time on study and signed informed consent .

4.2 Exclusion:

1. Patients with metastatic uveal melanoma
2. Patients with bone metastases only.
3. Patients with symptomatic brain or spinal cord metastases or requiring steroid therapy and patients with leptomeningeal disease. Patients with treated and stable CNS metastasis for 3 months or more, off steroids are eligible for the study. No major surgery or radiation therapy within 21 days before starting treatment.
4. Patients with significant cardiac illness such as symptomatic coronary artery disease or previous history of myocardial infarction, impaired left ventricle function (Ejection Fraction less than 50%) on account of any organic disease such as hypertension or valvular heart disease or serious cardiac arrhythmia requiring therapy. Patients with significant history of cardiac disease will be evaluated by the investigator or his designee.
5. Patients with significant impairment of pulmonary function on account of chronic bronchitis, emphysema or chronic obstructive pulmonary disease (COPD) which has resulted in impairment of vital capacity of FEV1 to less than 75% of predicted normal values.
6. Patients with symptomatic effusions on account of pleural, pericardial or peritoneal metastases of melanoma.
7. Patients who are unable to return for follow-up visits as required by this study.

Patients with a history of second malignant tumor, other than the common skin cancers - basal and squamous carcinomas, within the past 3 years and uncertainty about the histological nature of the metastatic lesions. Cases with other types of malignancies should be reviewed and decided by the PI of the study.

8. Patients with ≥ grade 2 sensory neuropathy at baseline.
9. Patients who have had major surgery or radiation therapy within 21 days of starting treatment.

5.0 Treatment Plan

5.1 Study Design

This is an open-label Phase II study to determine the efficacy and safety of ABI-007-Ipilimumab combination administered intravenously to patients with chemotherapy naïve metastatic malignant melanoma. Patients will be treated on an outpatient basis. All patients who sign an informed consent document and meet eligibility criteria must be registered and entered into the Clinical Oncology Research System (CORe). Baseline data must be entered before a cycle of therapy can be given. This study will be a single center, open-label, single-arm study to assess the safety and efficacy of ABI-007 plus Ipilimumab in patients with metastatic melanoma.

Baseline Assessments: Performed within 28 days of start of therapy. All patients must begin treatment within 7 days after registration.

- Treatment: Therapy will continue until disease progression or appearance of unacceptable toxicity.

5.2 Drugs and Dosages

Patients will be treated on an outpatient basis.

5.2.1 The rationale for the starting dose of ABI-007 and Ipilimumab

Phase I study of ABI-007 using weekly doses x 3 every 28 days has been completed in patients with metastatic breast cancer and melanoma. The results indicated that this dose schedule was better tolerated than ABI-007 administered by single dose every 21-day schedule. The optimum Phase II dose for the weekly x 3 q 28-day schedule was 150mg/m2 administered on days 1, 8, 15. A Phase III clinical trial comparing this dose schedule of ABI-007 to dacarbazine has been completed. The treatments were tolerated very well and the efficacy outcome of the trial will be announce in near future. **The starting dose of ABI-007 chosen for this trial is 150mg/m2 to be administered on days 1, 8, 15 every 28 days.**

The clinical experience with Ipilimumab in metastatic melanoma was recently reviewed.(17) The results of clinical trials with Ipilimumab used as single agent indicates that Ipilimumab used as single agent is most effective when delivered at the doses of 3-10 mg/kg. Ipilimumab has been given in combination with gp100 vaccine, dacarbazine, and IL-2 as 2 drug combination.(17) Currently, we are conducting a phase II study with Temozolomide plus Ipilimumab. Interim analysis showed that the combination is safe. In this trial, Ipilimumab will be given at the dose of 3mg/kg IV every 3 weeks for 4 doses only. The dose of Ipilimumab will not be increased.

5.2.2 Premedication

As hypersensitivity reactions are not expected, patients do not require premedication prior to ABI-007 administration. In the unlikely event of a hypersensitivity reaction, premedication may be administered using the premedication regimen the institution typically uses for Taxol. Antiemetics will be used regularly to control nausea and vomiting and may consist of Palonosetron 0.25 mg IV on days 1, 3, 5 or Zofran 16 mg IVPB daily until day 5 along with Ativan, 0.5-1 mg IV daily x 5 days. No premedication is needed for Ipilimumab.

5.3 Treatment

5.3.1 ABI-007

ABI-007 will be dosed intravenously over approximately 30 minutes without steroid pre-medication and without G-CSF prophylaxis (unless modified as described below).
ABI-007 at the dose of 150mg/m2 will be administered Weekly for 3 weeks every 28 days (+/- 3 days). The cycle length for ABI-007 is 28 days (+/- 3 day) ABI-007 will be administered before Ipilimumab on day one of every cycle that is concurrent with Ipilimumab. After administering ABI-007, wait 30 minutes, then administer Ipilimumab.

5.3.1 Ipilimumab:

Ipilimumab 3 mg/kg IV over 90 minutes on day 1. Ipilimumab dose will be repeated every 21 days (+/- 3 days) for a total of 4 doses. The cycle length for Ipilimumab is 21 days (+/- 3 days). The treatment cycles will be repeated as scheduled when the absolute neutrophil count has recovered to at least 750/mm^3 and platelets to 75,000/mm^3 and any other therapy related adverse event that may have occurred has resolved to $\leq$ Grade 1. A treatment cycle can be delayed up to 3 weeks.

After completion of Ipilimumab, ABI-007 will be administered alone at the same dose schedule.
Therapy will continue until disease progression or appearance of unacceptable toxicity.

5.3.1.1 Ipilimumab Dose Calculations

Calculate Total Dose as follows:
Patient body weight in kg x [*3 mg or study dose*] = total dose in mg
Calculate Total Infusion Volume as follows:
Total dose in mg ÷ 5 mg/mL = infusion volume in mL
Calculate Rate of Infusion as follows:
Infusion volume in mL ÷ 90 minutes = rate of infusion in mL/min.
For example, a patient weighing 114 kg (250 lb) would be administered 342 mg of Ipilimumab (114 kg x 3 mg/kg = 342 mg) with an infusion volume of 228 mL (342 mg ÷ 5 mg/mL = 69 mL) at a rate of approximately 2.5 mL/min, (69 mL ÷ 2.5 minutes) in about 25 minutes.

5.3.1.2 Storage, Preparation, and Administration

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

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

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

5.3.1.*3* *Preparation and Administration Guidelines*

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

1) As Ipilimumab is stored at refrigerated temperatures (2-8ºC), allow the appropriate number of vials of Ipilimumab to stand at room temperature for approximately five minutes.
2) Aseptically withdraw the required volume of Ipilimumab solution into a syringe. Insert the needle at an angle into the Ipilimumab vial by placing the needle – bevel side down – against the glass, with the tip touching the neck of the vial.
The initial solution concentration is 5 mg/mL. [Note: A sufficient excess of Ipilimumab is incorporated into each vial to account for withdrawal losses].
3) Ensure that the Ipilimumab solution is clear colorless, essentially free from particulate matter on visual inspection. If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall, etc.
4) Inject Ipilimumab solution withdrawn into an appropriate size evacuated infusion bag to produce a final infusion volume that has been calculated from the weight of the patient.
5) If the total dose calculates to less than 90 mL of solution then the total dose needed should be diluted to a total volume of 90 mL in 0.9% sodium chloride.
6) Mix by GENTLY inverting several times. DO NOT shake.
7) Visually inspect the final solution. If the initial diluted solution or final dilution for infusion is not clear or contents appear to contain precipitate, the solution should be discarded.
8) Do not draw into each vial more than once. Any partial vials should be safely discarded and should not be stored for reuse.

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

5.4 Dose Modification

5.4.1 ABI-007

If the first cycle of ABI-007 is not associated with grade one or higher toxicity, the patient will continue at the same dose level. There will be no further ABI-007 dose escalation for the subsequent cycles beyond 150mg/m2 weekly.

Dose reduction
ABI-007 Dose reductions will be permitted as outlined below. During the first cycle of therapy, to receive the day 8 and 15 Abraxane dose the patient must have ANC > 1000/mm3 and platelets > 75,000/mm3. If the ANC and platelets are not adequate for treatment on day 8 and/or 15, the dose will be omitted for that day and the total cycle length remains the same. If the ANC and platelets are not adequate on day 15, the dose will be omitted and that week will become the week of rest. The next dose (if counts and chemistries permit) becomes Day 1 of a new cycle, and the patient is considered to have had a 21 day cycle.
A maximum of two dose reductions will be allowed from the original dose to the following dose levels:

- 1st dose reduction; Level-1: ABI-007 dose will be decreased from original dose of 150mg/m2 to 120mg/m2 weekly
- 2nd dose reduction; Level-2: ABI-007 dose will be decreased from 120mg/m2 to 90mg/m2 weekly

ABI-007 cycles will be repeated at 4-week intervals as soon as the absolute neutrophil count has recovered to near 1500/mm3 and with a recovery of platelets to 100,000/mm3 and any other therapy related adverse event related to Ipilimumab has resolved to ≤grade 1 severity (except alopecia). ABI-007 dose modifications will be done based on degree of myelosuppression, renal, hepatic and neurologic toxicities as per standard guidelines. The use of hematopoietic growth factors to manage toxicities will not be allowed during Cycles 1 but will be allowed during subsequent cycles. The doses of ABI-007 and Ipilimumab will be adjusted to aim for an absolute neutrophil count of 500 ± 250/ul provided the platelet count is staying above 25,000/mm3 at nadir of myelosuppression. The dose adjustments will be as follows:

Dose level	ABI-007 mg/m2 days 1, 8, 15	Ipilimumab mg/kg day 1 only *
-2	90	3
-1	120	3
0	150	3

* If patient has grade 3 or 4 toxicity definitely related to Ipilimumab, then the Ipilimumab dose should be held until the toxicity resolves to ≤grade 1, then the dose should be reduced to 1mg/kg.

Patients who develop prolonged neutropenic fever or infection during neutropenia, will have their doses of ABI-007 reduced by 1 level. Growth factor for prevention of neutropenia is allowed as needed after the first cycle of therapy. Patients who develop significant peripheral neuropathy causing any evidence of ataxia or difficulty with function of the fingers such as writing or buttoning the clothes, will not receive any additional ABI-007. Development of moderately severe paresthesia will be used as a guideline to hold further therapy with ABI-007. Patients in whom ABI-007 therapy is discontinued will receive their subsequent doses of Ipilimumab therapy till the completion of 4 doses of Ipilimumab therapy.
If a toxicity requiring dose modification occurs following the second dose reduction, further treatment should be discontinued.

Rules for Dose Omissions and Modified Schedules for ABI-007 during second and subsequent cycles:

Day 1 dose missed:
If the dose held or missed was to be given on Day 1 of the next cycle, that next cycle will not

be considered to start until the day the first dose is actually administered to the patient

Day 8 dose is missed:
Cycle continues per protocol, with one dose not given, Day 15 is administered as per cycle calendar if counts and chemistries permit.

Day 15 dose missed:
That week becomes the week of rest. Next dose (if counts and chemistries permit) becomes Day 1 of a new cycle, and the patient is considered to have had 21-day cycle.

5.4.1.1 Administration of Study Drug to Patients with Abnormal Hematologic Function

Abraxane dosing should not be administered at the start of each cycle until the ANC count returns to >1500/mm3 and the platelet count retuns to > 100,000/mm3. For patients receiving weekly Abraxane, for each subsequent dose of Abraxane within a cycle (days 8 and 15) patients must have ANC > 1000/mm3 and platelets > 75,000/mm3. If the ANC and platelets are not adequate for treatment on day 8, the dose will be omitted and the total cycle length remains the same. If the ANC and platelets are not adequate on day 15, the dose will be omitted and that week will become the week of rest. The next dose (if counts and chemistries permit) becomes Day 1 of a new cycle, and the patient is considered to have had a 21 day cycle.

Colony Stimulating Factor Administration:
Colony stimulating factors may be given according to institutional guidelines for the treatment of neutropenic fever or infections associated with neutropenia. If a patient develops neutropenia after receiving study drug, the investigator may administer antibiotics as a prophylactic measure with subsequent cycles. All medications administered to a patient (e.g., growth factors, antibiotics, etc.) must be documented.

5.4.1.2 Dose Reductions for Non-hematologic Toxicity

HYPERSENSITIVITY REACTIONS
Minor symptoms such as flushing, skin reactions, dyspnea, hypotension, or tachycardia may require temporary interruption of the infusion. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema or generalized urticaria require immediate discontinuation of study drug administration and aggressive symptomatic therapy. Patients who develop severe hypersensitivity reactions to ABI-007 should not be re-challenged with the drug.

PERIPHERAL NEUROPATHY
ABRAXANE should be withheld in patients who experience Grade 3 sensory neuropathy. Treatment may be resumed at the next lower dose level in subsequent cycles after the sensory neuropathy improves to Grade 1. The time to resolution to Grade 1 should be the adverse event duration used for adverse event reporting. In those patients who experience Grade 4 sensory neuropathy, study drug should be withheld, and treatment resumed at a reduction of 2 dose levels in subsequent cycles after the sensory neuropathy improves to Grade 1. Note: the investigator may elect to dose modify for Grade 3 sensory neuropathy

CUTANEOUS TOXICITY
Patients who develop Grade 2 or 3 cutaneous toxicity should have their dose reduced by 1 dose level. If the patient continues to experience these reactions, despite dose reduction, treatment should be discontinued. Patients who develop Grade 4 cutaneous toxicity should have treatment discontinued.

GASTROINTESTINAL TOXICITY
If Grade 3 mucositis or diarrhea occurs, study drug should be withheld until resolution to Grade 1, then reinstituted at the next lower dose level. Patients who develop Grade 4 mucositis or diarrhea should have treatment discontinued.

OTHER NON-HEMATOLOGIC TOXICITIES
If toxicities are Grade 2, manage symptomatically if possible, and re-treat without dose reduction. If toxicities are Grade 3, treatment should be withheld until resolution to **Grade ≤ 1** or baseline if baseline was greater than Grade 1, then reinstituted, if medically appropriate, at the next lower dose level. Recurrence of a Grade 3 or 4 toxicity following 2 dose reductions will necessitate discontinuation of treatment.

Administration of Study Drug to Patients with Abnormal Hepatic Function:
Hepatic dysfunction that occurs while the patient is on study should prompt an evaluation to determine the cause, including the possibility of progressive metastatic disease and hepatotoxicity from concurrent medications. ABI-007 should not be administered if total serum bilirubin is > 1.5mg/dl.

Treatment for Brain metastases
Patients who develop brain metastases as their only sites of progressive disease may continue on this study after being treated (whole brain radiotheraphy, surgery or gamma knife) if they still otherwise continue to meet the eligibility criteria and if the investigator feels it is in the patient's best interest to continue on study. Therapy with study drug should be interrupted for at least 1 week after the patient has completed treatment for the brain metastases and has recovered from any associated side effects of treatment. For the purpose of data analysis, the date of progression for the patient will be the date the brain metastasis was documented radiographically or clinically.

5.4.1.3 Ipilimumab Recommended Dose Modifications permenately discontinue Ipilimumab for any of the following:

5.4.2 Ipilimumab

Ipilimumab cycles will be repeated at 3-week intervals as soon as the absolute neutrophil count has recovered to near 750/mm^3 and with a recovery of platelets to 75000/mm^3 and any other therapy related adverse event related to Ipilimumab has resolved to < grade 1 severity (except alopecia). Iplilimumab will be given every 3 weeks (+/- 3 days) for a total of 4 doses. Delay or cessation of Ipilimumab dosing will be instituted according to the specific irAE criteria as well as these NCI CTCAE (Version 4) criteria: Treatment modifications for suspected Adverse Reactions to Ipilimumab will be done based on the specific established pathways detailed in the appendices attached to the protocol.

Patients may develop study drug-related toxicities that may require skipping doses or dose discontinuation. If Ipilimumab dose is held or discontinued, continue the Abraxane therapy. Some of these adverse events may be consistent with potentially drug-related immune-mediated phenomena; termed irAEs including dermatitis, enterocolitis, hypophysitis, uveitis, hepatitis, and nephritis.
Enterocolitis, defined by grade 3/4 clinical presentation and/or biopsy documentation, was the most common dose-limiting major toxicity (21% of patients). (Appendix E). Details of how to dose study medication in the present of adverse drug reactions that may or may not be irAEs are addressed below.
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Ipilimumab Dose Modifications

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

Monitor thyroid function tests and clinical chemistries at the start of ipilimumab, before each dose and as clinically indicated based on symptoms. Withhold ipilimumab dosing in symptomatic patients, Initiate systemic corticosteroids at a dose of 1 to 2 mg/kg per day of prednisone or equivalent, and initiate appropriate hormone replacement therapy.

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

Delay Ipilimumab dosing for the following related adverse events:

- Any Grade 2 non-skin related adverse event (including IRAEs).
- Any Grade 3 skin-related adverse event (including IRAEs).

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

- If the adverse event has resolved, restart Ipilimumab dosing at the next scheduled time point per protocol.
- If the adverse event has not resolved in the protocol-specified dosing window (4 weeks [+/- 3 days], the next scheduled dose will be omitted.

5.4.2.1 Delay Ipilimumab dosing for the following related adverse events:

It may be necessary to skip study drug dosing for the following related adverse event(s):
Any ≥ Grade 2 non-skin related adverse event (including IBEs), except for laboratory abnormalities
Any ≥ Grade 3 laboratory abnormality.
It is necessary to skip study drug dosing for the following adverse events:
Any ≥ Grade 3 skin-related adverse event regardless of causality.
Restart Ipilimumab dosing if/when the adverse event(s) resolve(s) to ≤ Grade 1 severity or returns to baseline within 3 weeks of initial dose administration:
If the *adverse event has resolved,* restart Ipilimumab dosing at the next scheduled time point per protocol.
If the *adverse event has not resolved* in the protocol-specified dosing window (3 weeks [+/- 3 days], the next scheduled dose will be *omitted*.

5.4.2.2 Duration of Treatment

Patients who have not progressed after completing the 12 weeks of combination of ABI-007 plus Ipilimumab combination therapy, the patient may continue therapy with ABI-007 cycles alone every 4 weeks until they experience progressive disease or unacceptable toxicity, withdraw consent,
or the treating physician feels it is no longer in their best interest to continue on treatment. While receiving the therapy with ABI-007 alone follow-up evaluation with physical examination every 4 weeks and blood counts weekly, routine chemistry blood tests every 4 weeks and radiologic restaging to determine disease status should be performed every 8 weeks.

5.4.1.3 Discontinuation of Study Therapy

Subjects MUST be discontinued from study therapy AND withdrawn from the study for the following reasons:
Withdrawal of informed consent (subject's decision to withdraw for any reason):

Any clinical adverse event, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued treatment with study therapy is not in the best interest of the subject

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 frequency of on study pregnancy tests for WOCBP enrolled in the study.

¨ The investigator must immediately notify M.D. Anderson Cancer Center- IND office and BMS in the event of a confirmed pregnancy in a patient participating in the study. Termination of the study by the IND Sponsor-M.D. Anderson Cancer Center- IND office or by Celgene Corporation.

Permanently discontinue Ipilimumab for any of the following:

- Persistent moderate adverse reactions or inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day.
- Failure to complete full treatment course within 16 weeks from administration of first dose.
- Severe or life-threatening adverse reactions, including any of the following:
    - Colitis with abdominal pain, fever, ileus, or peritoneal signs; increase in stool frequency (7 or more over baseline), stool incontinence, need for intravenous hydration for more than 24 hours, gastrointestinal hemorrhage, and gastrointestinal perforation.
    - Asparate aminotransferase (AST) or alanine aminotransferase (ALT) >5 times the upper limit of normal or total bilirubin >3 times the upper limit of normal
    - Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations.
    - Severe motor or sensory neuropathy, Guillian-Barre syndrome, or myasthenia gravis.
    - Severe immune-mediated reactions involving any organ system (eg, nephritis, pneumonitis, pancreatitis, non-infectious myocarditis)
    - Immune-mediated ocular disease that is unresponsive to topical immunosuppressive therapy.

Exceptions to Permanent Discontinuation of Ipilimumab therapy
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.

Immune-Related Adverse Events (irAEs): Definition, Monitoring, and Treatment Blocking CTLA-4 function may permit the emergence of auto-reactive T cells and resultant clinical autoimmunity. Rash/vitiligo, diarrhea/colitis, uveitis/episcleritis, hepatitis, and hypopituitarism were drug-related, presumptive autoimmune events, now termed irAEs, noted in previous Ipilimumab studies.

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

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

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

5.4.1.4 Other Guidance

Treatment of Infusion Reactions Associated with Ipilimumab
Since Ipilimumab contains only human protein sequences, it is less likely that any allergic reaction will be seen in patients. However, it is possible that infusion of Ipilimumab will induce a cytokine release syndrome that could be evidenced by fever, chills, rigors, rash, pruritus, hypotension, hypertension, bronchospasm, or other symptoms. No prophylactic pre-medication will be given unless indicated by previous experience in an individual patient. Reactions should be treated based upon the following recommendations.
For mild symptoms (e.g., localized cutaneous reactions such as mild pruritus, flushing, rash):
¨ Decrease the rate of infusion until recovery from symptoms, remain at bedside and monitor patient.
¨ Complete the Ipilimumab infusion at the initial planned rate.
¨ Diphenhydramine 50 mg IV may be administered at the discretion of the treating physician and patients may receive additional doses with close monitoring.
¨ Premedication with diphenhydramine may be given at the discretion of the investigator for subsequent doses of Ipilimumab.
For moderate symptoms (any symptom not listed above [mild symptoms] or below [severe symptoms] such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic BP >80 mmHg):
¨ Interrupt Ipilimumab.
¨ Administer diphenhydramine 50 mg IV.
¨ Monitor patient closely until resolution of symptoms.
¨ Corticosteroids may abrogate any beneficial immunologic effect, but may be administered at the discretion of the treating physician.
¨ Resume Ipilimumab infusion after recovery of symptoms.

¨ At the discretion of the treating physician, Ipilimumab infusion may be resumed at *one half the initial infusion rate, then increased incrementally to the initial infusion rate.*
¨ If symptoms develop after resumption of the infusion, the infusion should be discontinued and no additional Ipilimumab should be administered that day.
¨ The next dose of Ipilimumab will be administered at its next scheduled time and may be given with pre-medication (diphenhydramine and acetaminophen) and careful monitoring, following the same treatment guidelines outlined above.
¨ At the discretion of the treating physician additional oral or IV antihistamine may be administered prior to dosing with Ipilimumab.

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

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

Treatment of Ipilimumab-Related Isolated Drug Fever

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

5.4.2 Concomitant Medications

Patients may not participate in any other clinical protocol or investigational trial that involves administration of experimental therapy and/or the use of investigational devices with therapeutic intent while enrolled in this study.
Radiotherapy, other than to control brain metastases is not allowed during the study.
Administration of other chemotherapy, immunotherapy, or anti-tumor hormonal therapy during the study is not allowed.
Supportive care, including but not limited to anti-emetic medications, may be administered at the discretion of the Investigator.
Concurrent treatment with bisphosphonates is allowed. Erythropoietin may be administered at the discretion of the investigator, consistent with institutional guidelines. G-CSF should be administered according to the institutional guidelines.

5.4.3 Drug Interaction

a- ABI-007

The potential drug-drug interactions precautions contained in the Abraxane prescribing information will be applied to this study (current version of Prescribing Information is provided in the Study Manual). Specifically, the metabolism of paclitaxel is catalyzed by cytochrome P450 isozymes CYP2C8 and CYP3A4. Caution is recommended when administering ABI-007 concomitantly with substrates or inhibitors of the cytochrome P450isozymes CYP2C8 and CYP3A4. Similarly, drugs, herbal preparations, and/or dietary supplements known to influence the expression of CYP3A (eg, phenytoin, rifampin, St. John's wort, garlic supplements, grapefruit juice) and/or CYP2C8 should be used with caution (see www.drug-interactions.com for a regularly updated list of drug interactions with cytochrome P450 isozymes).
The Abraxane prescribing information also cautions for potential interactions between paclitaxel, a substrate of CYP3A4 and protease inhibitors (ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4 and have not been evaluated in clinical trials.
Patients must be made aware that the following medications are not allowed to be taken concomitantly with ABI-007 monotherapy: ritonavir, saquinavir, indinavir, nelfinavir and doxorubicin, as well as any taxane, anthracycline, anti-cancer drug or other investigational study drug.
In clinical studies of ABI-007 performed to date, no steroidal premedication to reduce the risk of hypersensitivity reactions was necessary. No steroidal premedication is to be given to patients except as described below. If the investigator chooses to premedicate with an anti-emetic/anti-nauseant to prevent nausea and vomiting, medications such as Kytril and/or Compazine are suggested.
Hypersensitivity to Taxol has been attributed primarily to Cremophor® in the product, and is not therefore expected with ABI-007. However, if the patient experiences a typical Taxol hypersensitivity reaction manifested by flushing, lower back pain, and chest tightness, he/she should have their infusion stopped immediately. In the unlikely event of a mild hypersensitivity reaction, premedication may be administered using the premedication regimen the institution typically uses for solvent based paclitaxel. In the rare event of a severe hypersensitivity reaction, discontinue Abraxane.

b- Ipilimumab therapy

Patients in this study may not use vaccines for the treatment of cancer or prevention of disease unless indicated as a component of the protocol regimen (including those for common medical conditions) for up to one month pre and post dosing with Ipilimumab. Concomitant systemic or

local anti-cancer medications or treatments are prohibited in this study while receiving Ipilimumab treatments.
Patients may not use any of the following therapies during the study:
Any non-study anti-cancer agent (investigational or non-investigational)
Any other investigational agents
Any other (non-CA184024 related) CTLA-4 inhibitors or agonists
CD137 agonists
Immunosuppressive agents
Chronic systemic corticosteroids, although systemic steroids may be given to treat signs/symptoms of toxicities during the study, acute allergic reactions including and not limited to medications such as antibiotics, contrast media or asthma. Any non-oncology vaccine therapies used for the prevention of infectious diseases (for up to 30 days prior to or after any dose of study drug

5.4.4 Assessments
A- Clinical

Toxicity Assessments: Toxicity of treatment will be graded as per NCI common toxicity criteria for adverse events, version 4.0.

Response Assessments: ***Patients will be evaluated for complete response, partial response, stable or progressive disease every 8 weeks (+/- 7 days) from the start of treatment until progressive disease is documented.*** Tumor response to therapy in this study will be done using *immune-related response criteria (irRC)* which is a modified version of WHO criteria.

- Responders and stable disease patients will continue on study unless they develop unacceptable toxicity. Progressive disease or unacceptable toxicity will be the criteria for discontinuation of treatment. Patients who have not had progression of their cancer should continue to be followed with regularly scheduled tumor assessments with radiographic imaging until progressive disease is documented.

- End of Study (EOS) Evaluation: Physical examination (including vital signs: blood pressure, heart rate, respiration rate and temperature), weight, performance status, CBC/differential, platelet count, routine chemistry panel (must include ALT and AST, alkaline phosphatase, LDH, total bilirubin, and creatinine), toxicity assessment, concomitant medications, CT scan, and tumor measurements will be performed within 14 days of when the patient goes off-study treatment. For patients who have
- come off study for progression of disease, and restaging with all scans has been completed prior to the EOS visit, the scans will not need to be repeated within 14 days.

- Adverse Event Resolution Follow-up: Any adverse event (AE) that started any time beginning from the time of the first dose of study drug and ending 30 days after the last dose of study drug or EOS (whichever is later) will be followed.

- Follow-up for disease progression: Patients who are discontinued from treatment in the absence of disease progression (e.g. – patients removed for unacceptable toxicity) will undergo repeat imaging and tumor response assessments every 8 weeks until disease progression is documented. Patients who stop treatment prior to developing disease progression should be followed without further treatment until progressive disease is documented or until the treating physician feels additional treatment is required. In the latter case, there must be clear documentation as to the compelling reason(s) for starting a new treatment in the absence of progressive disease.

- Follow-up for Survival: Post study, patient survival status will be monitored on a bi-monthly basis for 6 months and every 3 months thereafter, for a total of 2 years post study. This evaluation may be by record review and/or telephone contact with the patients' treating physicians.

B- Laboratory

1- Evaluation of Molecular Biomarkers
Tumor biomarkers will be studied in an exploratory companion substudy to assess prognostic utility in identifying responders and non-responders. Molecular biomarkers will be assessed on archival paraffin-embedded (PE) tumor tissue and blood of patients entered into the trial who provide additional consent.

These biomarkers will include known mutations associated with melanoma may be examined in both tumor tissue and blood. The expression of molecular biomarkers such as SPARC and other mRNA expression profiles in PE tumor tissues will be assessed to determine its potential clinicopathological utility related to treatment with ABI-007. The objective will be to assess specific biomarkers that relate to treatment response and disease outcome. In addition, PE tissue sections will be obtained from tumor biopsy for immunohistochemistry (IHC) to assess SPARC and for molecular tumor biomarker validation.

Secreted Protein Acidic and Rich in Cysteine (SPARC)
SPARC (also known as osteonectin and BM40) is an albumin-binding protein that is overexpressed in over 70% of metastatic melanoma patients' tumors and is associated with a poor prognosis.
Albumin-binding proteins such as SPARC may play a role in the concentration of albumin-bound drugs, such as ABI-007, in the area of the tumor, and may be partly responsible for the greater activity of ABI-007 when compared to non-albumin-bound formulations. Tumor samples and peripheral blood will be collected from patients treated on this study to obtain preliminary data on a potential correlation between SPARC expression and response to therapy with ABI-007. In those cases where tumor samples from patients treated on this study are available and informed consent has been obtained, tumor samples will be submitted to a central laboratory for SPARC analysis. Samples will be run blinded to the treatment assignment

and to the response the patient had to treatment. Tumor biomarker analysis will be done on archived tissue or fresh tissue at baseline and again at time of progression of disease.

Information will be collected for the mutation status from those patients who had their tumor tested for B-RAF mutation prior to registration for this trial. For patients who did not have their tumor tested for B-RAF mutation, tumor tissue samples will be collected from skin metastasis for B-RAF mutation testing. Participation in tumor biopsy and these tumor specimen-based molecular biomarker analyses is optional.

In addition, we will attempt to evaluate blood biomarkers that have shown prognostic utility in monitoring patients during treatment . Blood samples will be used for monitoring the immunologic status of the patients during the therapy on this study.

2- Immunologic evaluations:
Venous blood samples will be collected at baseline, week 6, week 12, then every 12 weeks thereafter. During the maintenance phase, the venous blood samples will be drawn prior to the administration of IV Ipilimumab as an optional procedure. The 4 green top blood samples will be used to isolate PBMC and plasma for analysis in the laboratory as correlates of clinical response during the trial. We will use the PBMC to track changes in major lymphocyte (T-cell and NK cell) subsets to determine how activated the CD4+, CD8+, and regulatory T-cells (Tregs) change during treatment and how this correlates to response. The plasma will be used to monitor auto-antibody production using a defined set of auto-antigen targets previously defined in earlier Ipilimumab clinical trials by Dranoff and colleagues. The plasma will also be used to monitor changes in pro-inflammatory and anti-inflammatory cytokines (e.g., IL-1-beta, IL-2, IL-4, IL-6, IL-8, IL-10, TNF-alpha, IFN-gamma, GM-CSF, and VEGF). These will correlate eventually to clinical response.

6.0 Pretreatment evaluation

6.1 A complete history and physical, including vital signs, examination (including height, weight, and ECOG Performance Status) will be performed within 14 days prior to signing the informed consent document. Documentation of all visible or palpable sites of metastasis in the skin and lymph node bearing regions will be performed within 28 days of signing informed consent document which includes documentation of cutaneous lesions with the aid of a photograph to be filed in the chart.

6.2 A complete laboratory evaluation will be carried out and will include a CBC, differential, platelet count, sodium, potassium, chloride, CO2, BUN, creatinine, alk phosphatase, AST, ALT, LDH, total bilirubin, Mg, PT and PTT, and thyroid function tests (TSH, free T4) within 14 days of signing the informed consent document.

6.3 Staging work up will be carried out which will include a CT scan of the chest, a CT scan of the abdomen and an MRI or less preferably a CT scan of the brain within 28 days of signing the informed consent document. Patients with melanoma of the head and neck or with primary arising below the waist line will have also a CT scan of the neck and pelvis, respectively. For patients with significant extremity metastases (subcutaneous or other), MRI or CT of the relevant extremity is required.

6.4 Patients will have a baseline electrocardiogram within 28 days of signing the informed consent document. In case of abnormal results, the case must be discussed with the PI.

6.5 Patients with history of clinically significant chronic bronchitis or emphysema will have pulmonary function studies (FEV1 >65% or FVC >65%) within 6 months of signing the informed consent. In case of abnormal results, the case must be discussed with the PI.

6.6 Pregnancy test (blood or urine) will be performed within 72 hours of administrating Ipilimumab. If indicated, an FSH will be performed.

6.7 Concomitant medications and baseline toxicities will be documented within 14 days of signing the informed consent document informed consent document

6.8 Evaluation of Molecular Biomarkers
Patients with archival paraffin-embedded (PE) tumor tissue will have optional tumor biomarker study to assess prognostic utility in identifying responders and non-responders. These biomarkers will include known mutations associated with melanoma. The objective will be to assess specific biomarkers that relate to treatment response and disease outcome. In addition, PE tissue sections will be obtained from tumor biopsy for immunohistochemistry (IHC) to assess SPARC and for molecular tumor biomarker validation. Participation in tumor biopsy and these tumor specimen-based molecular biomarker analyses is optional. In addition, we will attempt to evaluate blood biomarkers such as SPARC that have shown prognostic utility in monitoring patients during treatment .

Optional Tumor Biopsies
Optional punch biopsies will be obtained from patients who have cutaneous lesions that are amenable to punch biopsies at two separate time-points. Optional biopsies are addressed in the consent and participants must have agreed to undergoing biopsies by signing and initialing this section in the consent. The first optional biopsy will occur at baseline prior to treatment. The second optional biopsy should occur on cycle 1 day 22 before the Ipilimumab infusion. Tissue samples should be placed in formalin and made into FFPE. Tumor tissue volume should be at least 125mm^3. The punch biopsy needle should be at least 5mm. The length of the biopsy should also be at least 5mm deep into the tumor. Half of the tumor will be analyzed for flow cytometry analysis and half for RNA isolation.

6.9 Evaluation of immune status:
Optional blood sample will be collected for evaluation of immune status prior to start of therapy.

7.0 Evaluation During Study

7.1 Physical examination, weight, vital signs, and concomitant medications will be assessed before each cycle (+/- 3 days).

7.2 The toxicity related to the treatment will be assessed before start of each cycle as per standard of care. Toxicity will be graded according to the NCI Common Toxicity Criteria (CTC), Version 4.0.

7.3 During the administration of ABI-007 plus Ipilimumab therapy, patients will have a CBC, differential, platelet count, sodium , potassium, chloride, CO2, BUN, creatinine, Alk Phosphatase, total bilirubin, LDH, ALT, AST, magnesium and pregnancy test (serum or urine) just prior to each cycle (+/-3 days). Thyroid function tests (TSH, free T4) are done before each dose of Ipilimumab and then every 3 months. (+/- 3 days). Following the administration of therapy, patients will be required to have a CBC, differential and platelets weekly (+/- 3 days). Weekly lab tests may be done at an outside facility. The research nurse or data coordinator will insure that the results are received and reviewed. Patients will be encouraged to bring a copy of the lab results to their clinic visit, if possible.

7.4 The size of the tumor (either in transit or palpable) will be monitored closely in order to assess response to treatment. Physical-measurements of the tumor will be done by the principal investigator or his designee before start of each cycle (+/- 3 days). Repeat CT of the affected area will done after 8 weeks (+/- 7 days) for assessment of response. For patients with skin lesions, photographs of the skin lesions will be done every 2 cycles. Chest x-ray will be done every 2 cycles. An MRI or CT scan of the brain will be repeated every 2 cycles to rule out the development of asymptomatic brain metastases. Thyroid function tests (TSH, free T4) every 3 months.

7.5 Immunologic and molecular monitoring: Venous blood samples will be collected for immunologic evaluation and molecular monitoring before cycle 1, 3 and odd numbered cycles as optional procedure. Not all optional samples may be collected at all time points and missed sample collections will not be considered protocol deviations. These will correlate eventually to clinical response.

Table 2: Time and Events Schedule for Protocol

Procedure	Pre-Therapy	Weekly	Every 3 Weeks	Every 4 Weeks	Every 8 Weeks	End of Treatment
Eligibility Assessments 1	X					
Informed Consent 1	X					
Inclusion/Exclusion Criteria 1	X					
Medical History 1,2	X			X		X
Physical Examination 1,2	X			X		X
Performance Status 1, 2	X			X		X
Height and Weight 1, 3	X			X		X
Physical measurements (in transit or palpable) 1	X			X		X
Vital Signs 1, 2	X			X		X
Concomitant Medications 1, 2, 4	X			X		X
Electrocardiogram	X					
Pregnancy Test 1, 5	X			X		
FSH 1	X					
Assessment of Toxicity 2, 6	X			X		X
Radiological Evaluation 7	X				X	X
Laboratory Tests 8	X	X		X		X
Thyroid Function Tests 8	X		X			
Ipilimumab Therapy 9			X			
Abraxane Therapy 9				X		
Tumor Biopsy 12	X					
Assessment of Response 10				X	X	X
Cytokine/Chemokine	X				X	X

11 (serum)						
Pulmonary Function Test 1	X					

1. Pre-treatment evaluations will be performed within 14 days prior to signing the consent form except pregnancy test and FSH (if indicated) which will be done 72 hours prior to first dose. Electrocardiogram within 28 days of signing consent form. PFT performed within 6 months of signing consent form.
2. Evaluations will be performed before each cycle of ABI-007 and Ipilimumab therapy (+/- 3 days) and at the discontinuation of therapy. They will Include blood pressure, pulse, respiration rate and temperature, weight, performance status. Vitals will be taken before the ABI-007 infusion, in between the ABI-007 and Ipilimumab infusion, and after the Ipilimumab infusion has completed prior to discharge. On days of ABI-007 infusion alone, vitals will be taken before the infusion and after completion of infusion prior to discharge.
3. Height (at pre-treatment only) and weight measurements.
4. Concomitant medications including those taken within 30 days prior to first dose of study therapy, during each cycle of ABI-007 therapy and those taken 30 days after last dose of study therapy.
5. A serum b-HCG or urine pregnancy test in women of child-bearing potential will be performed before every therapy cycle of ABI-007.
6. An assessment of baseline conditions and symptoms (including NCI-CTCAE grading for conditions present or ongoing prior to signing the consent form)
7. Imaging studies must be done within 28 days prior to signing the consent form. Photographic measurement of skin lesions are done when appropriate. For patients with known or suspected lymphadenopathy in the neck, contrast-enhanced CT of the neck is required. For patients with significant extremity metastases (subcutaneous or other), MRI or CT of the relevant extremity is required. MRI or CT scan of the brain is required prior the start of first therapy and every 8 weeks (+/- 7 days).
8. Pre-treatment blood samples will be collected before the 1st cycle of therapy. CBC is done weekly, liver and kidney profiles, electrolytes, magnesium are done before each cycle. Thyroid function tests (TSH, free T4) are done before start of Ipilimumab and before each dose of Ipilimumab and then every 3 months. (+/- 3 days). Labs may be done at an outside facility. The research nurse or data coordinator will be responsible for outside lab tests
9. ABI-007 plus Ipilimumab therapy will be given in the outpatient clinic . Abraxane cycle will be every 4 weeks, while ipilimumab cycle will be 3 weeks. On the weeks where ABI-007 and Ipilimumab are administered on the same day; ABI-007 will be administered first, wait 30 minutes after completion of ABI-007 infusion, then administer Ipilimumab
10. Tumor status assessment is done every 8 weeks (+/- 7 days) including photographic measurement of skin lesions, CT scans and/or MRI tumor assessments until documented tumor progression for patients who had a CR, PR, or SD, or discontinued study therapy due to toxicity or reasons other than progressive disease.
11. Blood samples should correlate with immunotherapy before treatment, during treatment and after treatment has completed.
12. Tumor biopsies will occur on baseline and cycle 1 day 22 prior to the 2nd Ipilimumab dose. Tumor biopsies will consist of punch biopsies on cutaneous lesions at two separate time-points. All biopsies are optional.

7.6 Physical examination (including vital signs: blood pressure, heart rate, respiration rate and temperature), weight, performance status, CBC/differential, platelet count, routine chemistry panel (must include ALT and AST, alkaline phosphatase, LDH, total bilirubin, and creatinine), toxicity assessment, concomitant medications, CT scan, and tumor measurements will be performed within 14 days of when the patient goes off-study treatment.

7.7 All drug-related toxicities must be followed until resolution. Patients are to be followed for 30 days (+ 7 days) after last drug administration for adverse events, regardless of causal relationship.

7.8 Survival data should be collected every two months (+/- 7 days) for 6 months and then every 3 months up to 2 years after the off treatment visit. Survival data will be collected by either telephone or by reviewing medical records for clinic visits. A record of the contact will be filed in the patient's chart and a copy of the record sent to scanned documents for inclusion in the patient's electronic medical record.

7.9 All relevant information regarding drug doses, concomitant medications and doses, measurable lesions, tumor response, laboratory examinations, and treatment-related toxicities shall be documented in the patient's medical record and flow sheets. The principal investigator or his collaborators will be responsible for tumor measurements and determine response whenever diagnostic imaging is performed.

8.0 Evaluation of response

8.1 Tumor response to therapy in this study will be done every 12 weeks (+/- 7 days) using *immune-related response criteria (irRC)* which is a modified version of WHO criteria.

8.1.1 Definition of Measurable and Non-Measurable Lesions

Measurable Lesions are lesions that can be accurately measured in two perpendicular diameters, with at least one diameter ≥20 mm and the other dimension ≥ 10 mm (10 mm x 10 mm for spiral CT). The area will be defined as the product of the largest diameter with its perpendicular. Skin lesions can be considered measurable.

Non-Measurable (evaluable) Lesions are all other lesions, including unidimensionally measurable disease and small lesions (lesions without at least one diameter ≥ 20 mm), and any of the following:

Lesions occurring in a previously irradiated area (unless they are documented as new lesions since the completion of radiation therapy), bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusion, lymphangitis cutis/pulmonis, abdominal masses that are not pathologically/cytologically confirmed and followed by imaging techniques and cystic lesions.
All measurable and non-measurable lesions should be measured at screening and at the defined tumor assessment timepoints. Extra assessments may be performed, as clinically indicated, if there is a suspicion of progression.

8.1.2 Definition of Index/Non-Index Lesions

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

lesions. In subsequent assessments, non-index lesions will be recorded as “stable or decreased disease,” “absent,” or “progression.”

8.2 Definition of Tumor Response Using irRC

The sum of the products of diameters at tumor assessment using the immune-related response criteria (irRC) 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.

8.2.1 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.

8.2.2 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).

8.2.3 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.

8.2.4 Definition of Overall Response Using irRC

Overall response using irRC will be based on these criteria:
Immune-Related Complete Response (irCR): Complete disappearance of *all* tumor lesions (index and non-index 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.

Table 3: Immune-Related Response Criteria Definitions

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

8.2.5 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 tumor assessment before 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.

8.2.6 Response Endpoints

Ipilimumab is expected to trigger immune-mediated responses, which require activation of the immune system prior to the observation of clinical responses. Such immune activation may take weeks to months to be evident. Some patients may have objective volume increase of tumor lesions or other disease parameters (based on study indication, ie, hematologic malignancies) within 12 weeks following start of Ipilimumab dosing. Such patients may not have had sufficient time to develop the required immune activation or, in some patients, 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.

Therefore, patients with tumor volume increase detected or lack of laboratory parameter response documentation prior to week 12 but without rapid clinical deterioration should continue to be treated with Ipilimumab and clinically observed with a stringent imaging schedule to allow detection of a subsequent tumor response. The treating physician will make the decision whether a patient should continue treatment or not although radiographic imaging may indicate progressive disease. This will improve the overall assessment of the clinical activity or Ipilimumab and more likely capture its true potential to induce clinical responses. Tumor assessments will be made using irCR which is a modified WHO criteria.

9.0 Evaluation of Toxicity

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

Safety will be evaluated for all treated patients using the
National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (http://ctep.cancer.gov). Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, physical examinations, and clinical laboratory tests.

ADVERSE EVENT REPORTING-BMS Reporting

9.1 Collection of Safety Information

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily 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 investigational product, whether or not considered related to the investigational product.

9.1.1 Serious Adverse Events

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

NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies:
a visit to the emergency room or other hospital department for less than 24 hours that does not result in admission (unless considered an “important medical event” or a life-threatening event) elective surgery, planned before signing consent admissions as per protocol for a planned medical/surgical procedure routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy) medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative). Note that all pregnancies, regardless of outcome, must be reported to BMS on a Pregnancy Surveillance Form, not an SAE form (Appendix G). All pregnancies must be reported and followed to outcome, including pregnancies that occur in the female partner of a male study subject.

9.1.2 Non-serious Adverse Events

All adverse events that are not classified as serious.

9.2 Assignment of Adverse Event Intensity and Relationship to Investigational Product

All adverse events, including those that are serious, will be graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE), Version 4.0. The following categories and definitions of causal relationship to investigational product as determined by a physician should be used for adverse events:
Certain: There is a reasonable causal relationship between the investigational product and the AE. The event responds to withdrawal of investigational product (dechallenge), and recurs with rechallenge when clinically feasible. Probable: There is a reasonable causal relationship between the investigational product and the AE. The event responds to dechallenge. Rechallenge is not required.

Possible: There is reasonable causal relationship between the investigational product and the AE. Dechallenge information is lacking or unclear. Not likely: There is a temporal relationship to investigational product administration, but there is not a reasonable causal relationship between the investigational product and the AE. Not Related: There is not a temporal relationship to investigational product administration (too early, or late, or investigational product not taken), or there is a reasonable causal relationship between non-investigational product, concurrent disease, or circumstance and the AE. The expression “reasonable causal relationship” is meant to convey in general that there are facts (eg, evidence such as de-challenge/re-challenge) or other arguments to suggest a positive causal relationship.

9.3 Adverse events for this protocol will be recorded according to the Recommended Adverse Event Recording Guidelines for a Phase II protocol. The investigator is responsible for verifying and providing source documentation for all adverse events and assigning attribution for each event for all subjects enrolled on the trial

Recommended Adverse Event Recording Guidelines					
Attribution	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

9.4 **ADVERSE EVENT REPORTING - M.D. Anderson Cancer Center and Celgene- Serious Adverse Event Reporting**

A serious adverse event is – any adverse drug experience occurring at any dose that results in any of the following outcomes:

· Death

· A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity – a substantial disruption of a person’s ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- **Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator, Celgene or the IND Sponsor.**

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the time frames and procedures outlined in “University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy on Reporting Serious Adverse Events”. Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IRB office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** expected or unexpected, and regardless of attribution to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to Celgene drug safety within 24 hours via email or fax using the information below:

  Celgene Corporation Drug Safety
  86 Morris Ave
  Summit, NJ 07901
  Toll free ; 800-640-7854
  Phone 908-673-9667
  Fax : 908-673-9115
  Email: drugsafety@celgene.com

  and the IRB office.

- The MDACC “Internal SAE Report Form for Prompt Reporting” will be used for reporting to the IRB office.

- Serious adverse events will be captured from the time the patient signs consent until 30 days after the last dose of drug. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IRB office. This may include the development of a secondary malignancy.

  Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager in the IRB office) according to 21 CFR 312.32.

- It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

9.4.1 Collection and Reporting

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

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

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

9.4.2 Serious Adverse Events

Following the subject's written consent to participate in the study, all SAEs must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 30 days of discontinuation of dosing of the investigational product. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy). The investigator should notify BMS of any SAE occurring after this time period that is believed to be certainly, probably, or possibly related to the investigational product or protocol-specified procedure.

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

All SAEs related to Ipilimumab 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 that meet the FDA reporting requirements should be reported on the MedWatch Form 3500A, which can be accessed at: http://www.fda.gov/Safety/MedWatch/HowToReport/ucm167733.htm. Fax: 1-800-FDA-0178 (1-800-332-0178)** The principal investigator or his designee will provide BMS with copies of all adverse events filed with the FDA.

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

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

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

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

9.4.3 Handling of Expedited Safety Reports

In accordance with local regulations, BMS will notify investigators of all SAEs that are suspected (certainly, probably, or possibly related to the investigational product) and unexpected (ie, not previously described in the Investigator Brochure). In the

European Union (EU), an event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). investigator notification of these events will be in the form of an expedited safety report (ESR).

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

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

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

9.4.4 Non-serious Adverse Events

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

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

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

9.4.5 Pregnancy

Sexually active WOCBP 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 WOCBP in this clinical study, the investigator 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.
Before study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during study 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 before receiving ipilimumab and ABI-007. 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 the investigational product, it is subsequently discovered that a study 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 (eg, dose tapering if necessary for subject safety). The investigator must immediately notify BMS of this event and record the pregnancy on the Pregnancy Surveillance Form (not an SAE form). Initial information on a pregnancy must be reported immediately to BMS, and the outcome information provided once the outcome is known. Completed Pregnancy Surveillance Forms must be forwarded to BMS according to SAE reporting procedures.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS, and Celgene.Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

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 to Celgene, and follow-up on information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants should be followed for a minimum of 8 weeks.

9.4.6 Other Safety Considerations

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

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

9.5 Collection and Reporting

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

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

10.0 Number of Patients

Simon's minimax two-stage design will be used to perform interim efficacy monitoring. It is assumed that the combination treatment will have a target PFS rate of 30%. A PFS rate of 15% or lower is considered a failure and the combination treatment will be considered as not having desired efficacy. With type I error of 0.05 and power of 90%, we will enter 42 patients in the first stage. If there are 6 or fewer patients who are alive and progression free at month 6, then the trial will be stopped and the combination treatment will not be considered for further study. If there are 7 or more patients who are alive and progression free at 6 months, 22 more patients will be enrolled and evaluated, giving us a total of 64 patients.

Primary Endpoints:

The primary efficacy objective of the study is to determine if the combination of ABI-007 plus Ipilimumab can delay disease progression in patients with metastatic melanoma. The primary efficacy endpoint is the rate of progression-free survival (PFS) at 6 months. Patients who are lost to follow-up or who are not evaluable at 6 months will be considered as failures (i.e., disease progression occurred). The 6-month PFS rate associated with the standard of care dacarbazine or temozolomide is about 15%, and we will target a PFS rate of 30% in this study.

Rationale for the primary endpoint:

The main goal of systemic therapy is to achieve complete remission when possible. The greater is the tumor regression; the better is palliation, improvement in quality of life and overall survival. Thus, it appears more appealing to use overall survival rather than response rate to assess the efficacy of systemic therapy, especially so with targeted therapies and immune response modifiers which show their beneficial effects slowly over time unlike the cytotoxic drugs. However, since patient death is observed quite late, after use of multiple regimens, any effect of the first line therapy has on the overall survival may be altered by the effects of subsequent therapies. The use of Progression Free survival (PFS) to assess benefit from an investigative agent makes the determination of the benefit from that therapy more accurate than that observed from use of overall survival. During the past couple of years, Meta-analysis of the outcomes of therapies of metastatic malignant melanoma (27) and colorectal (28) cancer were performed to determine if PFS is a better surrogate for survival in patients with these tumors. These studies concluded that PFS indeed offers a direct measure of new drug efficacy that is not obscured by subsequent therapies. It was postulated that, as more effective agents become available, PFS will become an even more desirable primary efficacy end point than overall survival. The advantage of determining the 6-month PFS rate rested in that ability to make early assessment of the agent in the trial, even if that agent showed its effect at a slower pace than cytotoxic drugs, as is the case with many targeted therapies and immunotherapeutic agents. Its use will reduce the sample size; shorten accrual time, and speed up the time of first analysis of treatment outcome.

We will also monitor the safety of the ABI-007 plus Ipilimumab combination treatment. Safety will be measured. We assume that response and toxicity are independent.

Efficacy Monitoring:

Simon's minimax two-stage design will be used to perform interim efficacy monitoring.(29) It is assumed that the combination treatment will have a target PFS rate of 30%. A PFS rate of 15% or lower is considered a failure and the combination treatment will be considered as not having desired efficacy. With type I error of 0.05 and power of 90%, we will enter 42 patients in the first stage. If there are 6 or fewer patients who are alive and progression free at month 6, then the trial will be stopped and the combination treatment will not be considered for further study. If there are 7 or more patients who are alive and progression free at 6 months, 22 more patients will be enrolled and evaluated, giving us a total of 64 patients. Accrual will be suspended after the 1st stage in the event where there are not at least 7 patients who are alive and progression free at 6 months and not all patients have been fully evaluated for the 6 months. Once a 7th patient has been observed to be alive and progression free at 6 months, accrual will be resumed. At the end of the study, if there are more than 14 patients who are alive and progression free at 6 months among the 64 patients, the ABI-007 plus Ipilimumab combination will be considered successful and will be considered for further study. If there are 14 or fewer patients who are alive and progression free at 6 months, then the combination will not be considered for future study. The early stopping probability is 55% if the PFS rate at 6 month is 15%.

Under the null hypothesis that the progression-free survival rate for the combination treatment is 15%, the trial will falsely conclude that it is effective 4.8% of the time. Under the alternative hypothesis that the progression-free survival rate is 30%, the study will falsely conclude that the combination treatment does not work 9.97% of the time.

Safety Monitoring:

The method of Thall, Simon, and Estey will be employed to perform interim safety monitoring.(30) We will assume a Beta (0.6, 1.4) prior distribution for the DLT rate on combination treatment, which in particular has mean DLT rate of 30%.

The following decision criteria will be applied with minimum of 3 patients, cohort size of 1, up to the 64th patient. Targeting a 30% DLT rate as a trade-off, the trial will be stopped early according to the following monitoring rule.

Pr{DLT rate > 30%| data} > 0.98

That is, if at any time during the study we determine that there is more than a 98% chance that the DLT rate in the combination treatment group is more than 30% we will stop the study. Stopping boundaries corresponding to this probability criterion are to terminate the trial if

[# of patients with DLT/ # of patients evaluated]:

≥ 4/4, 5/5, 6/7, 7/9, 8/12, 9/14, 10/16, 11/19, 12/21, 13/24, 14/26, 15/29, 16/32, 17/34, 18/37, 19/39, 20/42, 21/45, 22/48, 23/50, 24/53, 25/56, 26/58, or 27/61.

The operating characteristics of this rule in the trial are shown in the following table:

Operating Characteristics for Safety Monitoring Rule in the Study

True DLT Rate	Probability of Stopping Early	Sample Size		
		P25	Median	P75
10%	0 %	64	64	64
20%	0.6 %	64	64	64
30%	9.3 %	64	64	64
40%	52.7 %	25	60	64
50%	93.9 %	11	20	35

Statistical Analyses:

Descriptive statistics will be summarized for baseline characteristics of patients enrolled. Treatment administration will be summarized for each treatment cycle. Safety variables will be summarized by descriptive statistics. Adverse events and laboratory results will also be summarized in severity grade (CTCAE).

Tumor response will be evaluated based on immune-related response criteria (irRC) which is a modified version of WHO criteria. Progression-free survival will be estimated using the method of Kaplan-Meier. It will be determined from the start of the study until disease progression or death, whichever is first. All patients who do not have a disease progression or death will be censored on their last evaluable tumor assessment date. The PFS rate at 6 month will be provided with its 95% confidence interval estimated using bootstrap method. Median PFS will be reported together with a two-sided 95% CI calculated using the method of Brookmeyer and Crowley. Cox's proportional hazard model will be used to determine the relationship with PFS and the potential prognostic factors. Exploratory logistic regression will be used to identify the prognostic factors that are significantly correlated with PFS rate at 6 months.

We will also calculate the disease control rate (CR, PR, and stable disease) at 6 months for all the patients, together with its 95% confidence interval. Again, logistic regression will be used to determine the relationship between the disease control and the potential prognostic factors. Complete and partial tumor response rate as defined in section 9.2 of the protocol will also be provided, together with their 95% confidence intervals.

SPARC and Other Molecular Biomarkers
The correlation of SPARC and other molecular biomarkers with efficacy outcomes will be analyzed.

Response duration and overall survival will be estimated using the method of Kaplan-Meier method. The duration of response is measured from the date of first documentation of objective response (either complete or partial response, whichever is recorded first) to the date of first objective documentation of progression of disease according to the irRC criteria (taking as a reference for progressive disease the smallest measurements recorded since protocol therapy was initiated). The median and range of duration of response will be presented for subjects with a complete response, subjects with a partial response, and subjects with an overall response (i.e., confirmed complete or partial response). Overall survival is defined as the duration from the start of the study till death. If a patient is still alive at the end of the study, this patient will be censored on his last follow-up date. Median overall survival will be reported with their 95% CI. Cox's proportional hazard model will be used to estimate the relationship between overall survival and the same set of covariates used for PFS model.

11.0 Criteria for Removal from the Study

11.1 Progression disease associated with rapid clinical deterioration or development of new metastasis at a site that may be life threatening as judged by the treating physician at any time during therapy.
11.2 Development of unacceptable toxicity or patient's refusal to pursue further treatment.
11.3 Patients who have shown a systemic response and developed brain metastases as the only site of progression of disease may have the brain metastases treated and then resume the systemic therapy at the discretion of the study chairman.

Any serious adverse events will be reported to the Surveillance Committee at the M. D. Anderson Cancer Center. A serious adverse reaction includes any experience that:

Is fatal or immediately life-threatening
Is severely or permanently disabling
Requires or prolongs hospitalization
Is a congenital anomaly, cancer, or overdose.

Adverse Drug Reactions (ADRs) related to the study drugs are to be reported to the MDACC Surveillance Committee (IRB) within 10 working days of their occurrence. This includes all grade 4 and 5 toxicities except for grade 4 myelosuppression.

All serious, related adverse events will be reported and documented on Form FDA 3500 A (Med Watch Form) and forwarded directly to MGI Pharmaceuticals. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences.

12.0 References

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