A Phase 1 Study of HDAC Inhibitor PANOBINOSTAT (LBH 589) Administered in Combination with Ipilimumab in Subjects with Unresectable Stage III or Stage IV Melanoma

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TITLE OF STUDY:

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PRINCIPAL INVESTIGATOR:

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SPONSOR:

Moffitt Cancer Center

SYNOPSIS

Clinical Protocol MCC 17439

Title of Study: A Phase 1 Study of HDAC Inhibitor Panobinostat (LBH 589) Administered in Combination with Ipilimumab in Subjects with Unresectable Stage III or Stage IV Melanoma

Indication: Advanced Melanoma

Estimated Number of Study Centers and Countries/Regions: 1 site in the United States – Moffitt Cancer Center

Study Phase: 1

Research Hypothesis: We hypothesize that addition of a pan-HDAC inhibitor Panobinostat will be well tolerated and augment the clinical efficacy of ipilimumab.

The purpose of this study is to evaluate the safety profile, tolerability, and immunoregulatory (pharmacodynamic; PD) activity of Panobinostat administered in combination with ipilimumab (anti-CTLA4 antibody) to subjects with unresectable Stage III or Stage IV melanoma.

Primary Objective:
- To define the safety, tolerability, dose-limiting toxicities (DLTs), maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of Panobinostat administered in combination with ipilimumab in subjects with unresectable Stage III or Stage IV melanoma

Secondary Objectives:
- To describe the preliminary anti-tumor activity of panobinostat administered in combination with ipilimumab to subjects with unresectable Stage III or Stage IV melanoma
- To monitor trough concentrations of ipilimumab administered in combination with panobinostat
- To evaluate the pharmacodynamic (PD) effect of the combination dose regimen on biomarkers in peripheral blood samples and tumor biopsy specimens

Exploratory Objectives:
- To explore potential relationships between panobinostat exposure, biomarker measures, anti- tumor activity and adverse event, for the combination dose regimen

Study Design: This is a Phase 1, open label, dose escalation cohort study. The study will consist of a dose escalation assessment of the safety and tolerability of panobinostat administered concurrently in combination with ipilimumab to subjects with advanced melanoma. Treatment will be divided into induction and maintenance phases.

It is anticipated that this clinical study will enable selection of the RP2D and dose schedule of this combination for further clinical testing. The trial will include an assessment of the PD activity of panobinostat administered in combination with ipilimumab. A study schematic is presented below:

Each treatment cycle will be 42 days (6 weeks) during the induction phase, and 84 days (12 weeks) during the maintenance phase. Panobinostat will be administered orally thrice weekly (TIW) on Days 1-42 of each 42-day treatment cycle. Ipilimumab will be administered intravenously (IV) over 90 minutes on Days 1 and 22 of each treatment cycle. The induction phase will last for 2 treatment cycles. During the maintenance phase, panobinostat will be administered orally thrice weekly on Days 1-84 of each 84 day treatment cycle. Subjects will continue maintenance treatment with their panobinostat dose regimen until progression of disease, discontinuation due to toxicity, withdrawal of consent or any other reason as specified in Section 3.4.

Dose escalation: This is a modification of the traditional 3+3 design. Subjects will be enrolled in successive cohorts of 6. An initial cohort of 3 subjects will be enrolled at the given dose level of panobinostat, and additional subjects will be added to the same dose level (eg, increase the total number of enrolled subjects from 3 to 6, 9 or 12) based on a modified version of a toxicity probability interval (TPI) design. The modified TPI (mTPI) design uses Bayes rule in a decision theoretic framework to determine the MTD based on a pre-specified

target toxicity (eg, dose limiting toxicity; DLT) probability p_T. A fixed total number of subjects will be used during the dose escalation portion for each arm. As the dose escalation proceeds under this design, the number of subjects enrolled at a given dose level depends on the number of the toxicities observed at that dose such that multiples of 3 subjects each may be enrolled to enable a dose escalation decision. The MTD is selected as the dose with an observed toxicity rate closest to the pre-specified target toxicity probability P_T. In this study, a tight 18% target toxicity (P_T) is used.

Dose escalation will evaluate panobinostat at doses ranging from 5 to 20 mg thrice weekly administered in combination with ipilimumab at doses of 3 mg/kg. The first cohort will receive panobinostat orally at a dose of 5 mg thrice weekly; ipilimumab will be administered IV at a dose of 3 mg/kg. Enrollment will proceed with administration of escalating doses of panobinostat in combination with ipilimumab as described in Table 1 below:

Table 1 Dose Escalation regimen for Panobinostat and Ipilimumab

Dose Cohort	Panobinostat Dose	Ipilimumab Dose
1	**5 mg po TIW**	**3 mg/kg**
2	**10 mg po TIW**	**3 mg/kg**
3	**15 mg po TIW**	**3 mg/kg**
4	**20 mg po TIW**	**3 mg/kg**
-1	**5 mg po TIW**	**1 mg/kg**

Additional dose levels of panobinostat beyond 20 mg thrice weekly dose cohort may be added if appropriate based on the safety and tolerability profile of the combination, and after consultation and agreement between Investigators and Novartis. It is expected that all subsequent dose levels of panobinostat will be no more than 33% higher than the preceding dose. If cohort 1 shows unacceptable toxicity, then cohort -1 will be tested as indicated in table 1. **There will be no intra-subject dose escalation**. Decisions regarding dose escalation between individual dose levels will be guided by the incidence of drug-related dose limiting toxicities (DLTs) occurring within 84 days (12 weeks; through Day 42 of induction cycle 2) of initiation of study therapy. This observation interval is based upon inclusion of the known median times to onset of common immune-related adverse events attributed to ipilimumab (Section 4.3.3.1) and allows for a substantial amount of time for unexpected toxicities with the combined administration of panobinostat and ipilimumab to emerge. Subjects who do not complete the DLT observation period for reasons other than drug-related toxicity will be replaced.

One of the following five decisions will be made at the end of the DLT period for each cohort of 3-6 or more subjects if required based on the number of DLTs observed:

S: stay at the same dose and enroll a cohort of 3 more subjects at that dose E: escalate to the next higher dose by enrolling 3 more subjects D: de-escalate to the lower dose, and enroll 3 more subjects at that dose, DU: declare the current dose as unacceptable and unsafe, de-escalate to the lower dose, and enroll 3 more subjects at the lower dose, or C: Study completed and dose is declared to be the MTD

Note that decisions S or E are allowed by the design when determined that the corresponding doses are safe based on the target toxicity. Decisions D or DU are based on evidence of exceeding predetermined toxicity. With a target toxicity rate of 18%, allowing any dose with estimated P_T in the (17%, 19%) interval to be selected as the MTD in this study, and with a maximum fixed total of 12 subjects at the dose escalation phase in each arm, the algorithm for dose escalation decisions based on possible total number of subjects at each dose cohort is described in Table 3.2.

Based on the above design, escalation to the next higher dose level can occur if DLTs are observed in 0 of 3 or 1of 6 subjects, in up to 2 of 12 subjects, and so on. If DLTs are observed in a greater number of subjects and escalation is not yet permitted, additional subjects in cohorts of 3 will be enrolled at the same dose in order to better estimate the true DLT rate at that dose until either the dose is deemed safe and an escalation is allowed, the dose is deemed unacceptable and should not be used, or de-escalation is recommended, based on decision rules outlined in Table 3.2. At the end of the dose escalation phase, the MTD will be estimated by isotonic regression or another Bayesian model-based approach (eg logistic regression) using observed toxicities at all studied doses.

The combination dose with posterior probability of toxicity closest to the target toxicity, P_T, will be declared as the MTD.

The dose escalation plan (see table above) uses a modified Ji design, with dose escalation decisions made every three patients. The trial will enroll 36 patients for determination of the MTD, but will be successfully concluded earlier if 12 patients are accrued at the dose determined to be the MTD, with at most 3 toxicities.

De-escalation. The dose escalation plan (Table 1) follows a simple order restriction, that is, each dose cohort is as high or higher in both doses compared to all lower cohorts. While cohort -1 is below cohort 1, its relative unacceptable toxicity rate is unclear. If de-escalation from cohort 1 is needed, it will go to cohort -1. As long as the decisions are to "stay" at the same dose, cohort -1 will be grown to match that of cohort 1, and then they will be alternated. If for the same number of patients treated, the toxicity differential between them reaches 2, the other cohort will be dropped from further study. It is possible that both cohorts could be considered "the MTD". In such an event, other features such as patient response would be used to determine which would be the recommended phase 2 dose (RP2D). If the MTD is a unique cohort, that will also be called the RP2D.

This phase I study design has tended to be applied to a fixed sample size of 30. Due to the increased complexity of this combination-dose trial, we have chosen a sample size of 36.

All available clinical and laboratory data, and the nature, time of onset and time to resolution of DLTs observed during dose escalation will be reviewed to determine whether an alternate dose schedule should be examined after consultation between the Investigators and Novartis if needed. If agreed upon, the alternate schedule will be identified by a protocol amendment and the MTD determined for the revised dose schedule.

In addition to the Investigator's review of study data, the existing Moffitt Protocol Monitoring Committee (PMC) will be utilized to advise on aggregate safety data from this study and more specifically to review all Grade 3 or greater immune-related adverse events (irAEs).

Dose Limiting Toxicity: For the purpose of guiding dose escalation decision making, hematologic and non-hematologic (hepatic versus non-hepatic) DLT will be defined separately and will be determined based on the incidence, severity, and duration of study drug-related AEs occurring within 84 days (12 weeks; through Day 42 of induction cycle 2) of initiation of study therapy. For the purposes of subject management, DLTs will lead to dose modification regardless of the cycle in which a DLT occurs (see Section 4.3.6 for specific guidelines).

Duration of Study: It is expected that approximately 24 months will be required to complete enrollment in the study. Subjects may discontinue from treatment because of disease progression, unacceptable toxicity, withdrawal of consent, or at the discretion of the Investigator. The last visit for each subject will be defined as the follow up visit which is no less than 90 days after the subject's end-of-treatment visit. The last visit is either 90 days after last dose or whenever a study drug related toxicity has resolved, stabilized, or been deemed reversible, whichever is latest. The end of the trial will occur on the last visit of the last patient.

Number of Subjects: A total of up to 36 subjects are expected to be treated on the study.

Study Population: Male and female subjects ≥ 18 years of age with a histologic or cytologic diagnosis of unresectable Stage III or Stage IV melanoma and who meet the eligibility criteria (see Sections 3.2.1 and 3.2.2) will participate in the study.

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Panobinostat is available as 5, 10, 15, and 20 mg capsules and will be administered orally. Ipilimumab is available as sterile dose formulation at 5 mg/mL and will be administered intravenously (IV) as an infusion over 90 minutes. Ipilimumab is not to be administered as an IV push or bolus injection. Panobinostat will be administered at 5, 10 mg, 15 mg, or 20 mg thrice weekly in combination with ipilimumab administered at a dose of 3 mg/kg according to the dose schedule in Table 1. Panobinostat doses beyond 20 mg PO TIW may be considered if appropriate as outlined under study design.

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Study Assessments and Primary Endpoints: Subjects will be required to visit the investigator's office or clinic for physical examinations, vital sign measurements, ECOG performance status evaluation, adverse event

assessment, laboratory testing, pharmacodynamic (PD) sample collection, and administration of study drug as per the study schedule.

- **Safety Outcome Measures**: All subjects who receive study drug therapy will be evaluated for safety. 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. Triplicate 12-lead electrocardiograms (ECGs) will be collected prior to dosing on Day 1 of induction cycle 1. Single 12- lead ECGs will be collected at screening, prior to dosing on Day 1 of all treatment cycles (with the exception of induction cycle 1 as above) and at the end of treatment.

Adverse events will be categorized using the most current version of MedDRA and adverse events and laboratory tests will be graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Hepatic adverse events (AST, ALT, T Bili) will also be recorded relative to ULN. Immune-related adverse experiences (irAEs) among treated subjects will be specifically assessed as well.

- **Efficacy Measures:** Tumor response will be determined for all subjects by RECIST 1.1 (see Appendix 3) as well as by immune-related response criteria (irRC; see Appendix 4). RECIST 1.1 will be used for statistical analysis of efficacy in this study. Treatment decisions related to subject management may be based on the irRC criteria, but for the purposes of reporting efficacy RECIT 1.1 criteria will be used. Assessments of tumor status will be made during screening, then at 6 weeks and 12 weeks, and subsequently every 12 weeks. Tumor assessments at the end-of-treatment (EOT) or 90-day follow-up visit will be performed only if not assessed within the prior 12 weeks. Individual subject's best overall response (BOR) will be assessed, and progression free survival (PFS) will be calculated by RECIST 1.1 response criteria. Other endpoints are Objective response (OR) defined as BOR outcome of CR or PR for RECIST 1.1, disease control (DC) defined as BOR outcome of CR, PR, or Stable Disease by RECIST 1.1. Duration of response and duration of disease control will also be calculated.

Statistical Methods:

Sample Size Determination:

Dose Escalation: This is a Phase I dose escalation trial and the sample size at each dose depends on the observed toxicity. A total of 36 subjects at the dose-escalation phase allows sufficient number of subjects if needed, e.g. more than 6 subjects if dose-limiting toxicities are observed among 2 of 6 subjects, to better estimate the toxicity rates per dose, and more accurately determine the MTD. Cohorts of 3 subjects with possible expansions to 6, 9, or 12 subjects will be treated at each suggested dose level until MTD is defined.

Statistical Analysis: Safety Analyses: All recorded adverse events will be listed and tabulated by system organ class, preferred term, and dose and coded according to the most current version of MedDRA. The incidence of adverse events will be tabulated and reviewed for potential significance and clinical importance. Vital signs and clinical laboratory test results will be listed and summarized by dose. Any significant physical examination findings and results of clinical laboratory tests will be listed. ECG listings will be evaluated by the investigator and abnormalities, if present, will be listed. A separate listing and summary of all immune-related adverse events (irAE) and inflammatory events regardless of causality (IERC) will be provided. In addition, the irAE rate will be estimated and a 90% confidence interval will be constructed for the irAE and the grade 3-4 GI irAE rate in each arm, based on the Clopper-Pearson method. The relationship between panobinostat exposure/dose and adverse event may be explored graphically and appropriate model may be fit.

Efficacy Analyses: Listings of tumor measurements will be provided by subject and study day in each arm. Each individual subject's best overall response (BOR) and progression free survival (PFS) will be listed based on RECIST 1.1 (all subjects during dose escalation and cohort expansion portions of the study).
To describe the anti-tumor activity of panobiostat administered in combination with ipilimumab, Objective Response Rate (ORR) will be tabulated and estimated by 90% confidence intervals based on Clopper-Pearson method. Disease Control Rate (DCR) will be similarly summarized. Duration of response and duration of disease control will also be calculated for the subjects with such outcome, based on both efficacy criteria.

For all patients, duration of response, and duration of disease control will be estimated by Kaplan-Meier method and with 95% confidence intervals based on both response criteria. Kaplan Meier plots will be provided for all time-to-event variables at the MTD of each arm, based on both response criteria. We will also fit the survival function using a parametric survival approach, as this approach provides a more accurate estimate of the median PFS. The above analyses will include subjects from the dose expansion as well as subjects from the dose escalation portion who were treated at the MTD. Additional assessments eg, sensitivity analyses may be provided to assess clinical activity. The relationship between panobinostat exposure/dose and clinical efficacy (e.g. tumor response based on both RECIST 1.1 criteria) may be explored graphically and appropriate model may be fit.

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1 INTRODUCTION AND STUDY RATIONALE

1.1 Study Rationale

1.1.1 Rationale for Subject Population Selection for the Study

Since 1950, the global incidence of malignant melanoma has risen 690% while mortality rate increased by 165%. Even with the recent decline in the incidence of several cancers, the incidence of malignant melanoma is continuing to rise.[1] While overall survival has improved for early stage tumors because of early detection and improved surgical treatment, recurrent and/or metastatic malignant melanoma remains largely a fatal disease. High-dose interferon alfa-2b (IFN) is currently approved by US Food and Drug Administration (FDA) for use as adjuvant therapy in patients with high risk of relapse. Treatment with high-dose IFN is, however, associated with only 10% improvement in recurrence-free survival, 0-10% improvement in overall survival and very significant toxicities that limit compliance with its use[2,3,4] Dacarbazine, an FDA and EU approved chemotherapeutic agent for metastatic melanoma, provides an objective tumor response in only 5% to 20% of patients. These responses are short-lived (median duration of response = 6 months), and there is no associated increase in survival.[5] High-dose IL-2 therapy is also approved for use in the metastatic setting. However, significant toxicity limits its clinical utility. Fotemustine, with an overall response rate of 15%, 6 months median duration of response and 2 months median time to progression, is approved in parts of EU for use in patients with metastatic melanoma.[6] Over the last 30 years many chemotherapeutic drugs, including the aggressive Dartmouth combination regimen (dacarbazine, cisplatin, carmustine, and tamoxifen)[7] and newer drugs such as temozolomide,[8] have been explored but have not resulted in significant improvement in survival when compared to dacarbazine. In fact, only one agent to date has been shown to extend survival in metastatic disease, the CTLA-4 abrogating antibody ipilimumab. In two phase III randomized trials, one in previously treated disease, and one in untreated stage IV melanoma, ipilimumab prolonged survival compared to either a vaccine alone cohort in pre-treated patients, or with chemotherapy compared to chemotherapy alone in untreated patients [9, 10]. Malignant melanoma continues represent a considerable unmet medical need based on the significant but moderate efficacy and moderately severe toxicities of ipilimumab alone and the rising incidence of the melanoma in the world-wide.

Molecular profiling studies in melanoma subjects have demonstrated that tumors in 40 to 60% of subjects harbor activating mutations in BRAF. The V600E mutation is most common and accounts for greater that 80% of all mutations seen in BRAF.[11-13] Suppression of activating BRAF mutations in human melanoma cells results in inhibition of the MAPK/ERK cascade causing growth arrest and promoting apoptosis.[14,15] These and several other preclinical studies supporting an important role of MAPK signaling in melanoma have provided a strong scientific rationale for RAF as an important target in melanoma. Several selective RAF and MEK small molecule inhibitors are being tested at present in Phase 1 and Phase 2 clinical trials. Among these, R05185426 (PLX4032, Vemurafenib), a selective inhibitor of V600E mutant B-RAF kinase, has already demonstrated significant antitumor activity and high response rates in B-RAF V600E mutation positive melanoma subjects in Phase 1 and Phase 2 studies.[16] At ASCO 2011, the first results of a randomized phase III trial of vemurafenib compared with Dacabazine showed that both overall survival and relapse-free survival were significantly prolonged in the vemurafenib group compared to the chemotherapy control arm[17, 18] These observations have established B-RAF inhibition as a

legitimate therapeutic target in melanoma, but there are still significant unmet needs in unresectable melanoma, since most patients treated with vemurafenib will ultimately progress within 12 months, and at least 50% of all stage IV melanoma patients will have no chance to benefit from a B-RAF inhibitor.

As is outlined in Section 1.4.1 below, panobinostat is a potent and selective inhibitor of histone deacetylase (HDAC)[19-24]. Pre-clinical data from [redacted] laboratory at Moffitt indicate that HDAC inhibitors including LHB589 have unexpected activity as immunomodulatory agents, with impact on the in vitro activity of antigen presenting cells, decreased immune-inhibiting cytokines from tumor cell lines, and decreased immune inhibition of effector T cells. Additional work in his laboratory has shown that in in vivo animal models of the poorly immunogenic B16 melanoma, addition of panobinostat can augment the clinical benefit of ipilimumab. Data from other laboratories, including [redacted] showed that the addition of a pan-HDAC inhibitor (LAQ824) augmented the anti-tumor activity of adoptively transferred cytolytic T cells that were melanoma antigen-specific[25] Further work using panobinostat in vitro has shown that inhibition of STAT3, changes in CCL22 that allow for Th1 polarization, and decreases in IL-6 and other immunosuppressive cytokines may have a beneficial effect upon the use of immune modulators like ipilimumab when used in melanoma[10]. Taken together, these data indicate that testing whether an HDAC inhibitor like panobinostat adds to the immune and clinical effects of ipilimumab in patients with melanoma is warranted.

Malignant melanoma is also an immune responsive disease. The earliest evidence provided by epidemiological observations that immunosuppressed patients have an increased incidence of melanoma, and in some (<1%) immunocompetent patients the primary melanoma lesions spontaneously regressed. Infiltration of melanoma lesions by T lymphocytes has been shown to be associated with a better clinical prognosis.[26] Advances in immunology and oncology have revealed a dynamic interplay between host and tumor, suggesting that the ability of the tumor to evade the immune response can be an important determinant of the clinical course of the disease.20 Immunologic interventions to treat cancer can potentially be achieved through the induction of an immune response (active immunotherapy), administration of antibodies (passive immunotherapy), and/or stimulation of effector cells with cytokines or antibodies (immunostimulation). These approaches have resulted in the therapeutic use of immune- modulating agents such as IFN-α and IL-2 for the treatment of melanoma. In addition to a direct cytotoxic effect, IFN-α has also been demonstrated to stimulate natural killer (NK) cell activity and to regulate the expression of histocompatibility antigens or tumor- associated antigens.[27] Similarly, IL-2 modulates the immune system by stimulating the growth and activity of T lymphocytes, human lymphocyte antigen (HLA)-restricted or -non-restricted cytotoxic T cells and induces the production of many cytokines, such as tumor necrosis factor (TNF), IFN-γ and IL-1.[28] Ipilimumab, an antibody that abrogates the regulatory activity of cytotoxic-T lymphocyte antigen-4 (CTLA-4) on T cells and augments T cell proliferation, lytic activity and secretion of IL-2, has been shown to have anti-tumor activity in melanoma, renal cell cancer and other histologies [29-32].

Ipilimumab has been tested extensively at doses of 3 mg/kg given as induction treatment four times over 12 weeks, or at 10 mg/kg given as induction therapy over 12 weeks, followed by maintenance therapy every 12 weeks until progression or relapse in patients with metastatic melanoma [33-34]. The results of a phase III randomized trial of ipilimumab alone at 3 mg/kg or with a peptide vaccine compared with vaccine alone have been described, showing that

ipilimumab significantly prolongs survival in previously treated patients with advanced melanoma compared to the control arm.[35] The median OS for patients receiving ipilimumab alone or with a peptide vaccine was 10.1 and 10.0 months, respectively, compared with 6.4 months for the vaccine-alone control arm (P = .003 and P < .001, and hazard ratios of 0.66 and 0.68, compared with vaccine alone). In that trial, the rate of grades 3-4 dose limiting side effects was 8.1%, with the majority of events being immune related adverse events (irAEs) related to the immune mechanism of action of ipilimumab. Predominant events were skin related, colitis, hypophysitis and hepatitis. Virtually all dose limiting and other toxicities were reversible with the use of systemic steroids or in rare cases the TNF blocking antibody Infliximab. Recently, the results of a large placebo-controlled phase III study in 502 patients treated with first-line DTIC with or without ipilimumab (10 mg/kg) were presented and published[10]. In that trial, survival was prolonged in the ipilimumab+DTIC containing arm compared to chemotherapy alone with p=0.0009 and a hazard ratio of 0.72 favoring ipilimumab+DTIC. Median survivals in that trial were 11.1 months for the ipilimumab arm versus 9.1 months for the control chemotherapy cohort. The safety data from that first-line trial confirmed that incidence of irAEs was indeed dose related but also determined by the ipilimumab partner, since in that trial grades 3-4 colitis was uncommon, at less than 6%, grades 3-4 hypophysitis was not seen, but elevated ALT/AST was quite common, observed in 18-21% of patients in the ipilimumab+DTIC cohort. Of note is that grades 3-4 elevation of ALT/AST has been seen at a rate of 2% or less in trials of ipilimumab at 3 or 10 mg/kg alone. Nonetheless, ipilimumab at 10 mg/kg was felt to be well tolerated with DTIC, and when tested alone, dose limiting irAEs were observed in approximately 20% of patients[33-34]. As in the second line trial at 3 mg/kg described above, at a dose of 10 mg/kg, virtually all ipilimumab associated irAEs were rapidly reversible with systemic steroids and rarely the use of TNF-blocking antibody infliximab. No treatment related deaths were observed in the ipilimumab + DTIC group. Two additional trials provide further support of the likelihood that ipilimumab at 3 mg/kg will be well tolerated with another immune modulator In a trial of high dose interleukin 2 and ipilimumab, the drugs were given at a dose of 720,000 IU/kg and 3 mg/kg respectively repetitively[36]. The overall irAE rate of 14% was similar to that for ipilimumab alone at 3 mg/kg, and no treatment related deaths were reported, but a 22% ORR was described. Tarhini et al described follow-up data of from 36 patients in a trial conducted with the other CTLA-4 antibody from Pfizer, tremelimumab at 15 mg/kg, administered concurrently with high dose interferon alpha 2b[37]. In that trial, grade 3-4 dose limiting colitis was seen in 14% of patients, and grade 3-4 ALT-AST in 11%, not different than that seen with tremelimumab alone at that dose. These data suggest that ipilimumab at doses of 3 mg/kg will be well tolerated, and that given the collective expertise of the principal and co-investigators of this trial with the drug, the risk of significant and dose limiting side effects with the combination of ipilimumab and LBH589 will be minimized.

Considered together, the observations summarized above suggest that a therapeutic regimen combining a HDAC inhibiting agent capable of immune modulation with an immune-stimulating agent designed to potentiate the host antitumor response would be a rational, novel and well tolerated approach for the treatment of melanoma. It is likely that a HDAC inhibitor such as panobinostat could potentiate the antitumor immune response induced by ipilimumab by virtue of inducing important immune stimulating cytokines, decreasing levels of immune suppressive cytokines, increasing APC's function and enhancingT-cell responses by epigenetic modulation of critical transcription factors (ie, EOMES). A careful phase I dose escalating trial is planned to evaluate biologic endpoints as well as the toxicity of the combination regimen.

1.2 Research Hypothesis

The purpose of this study is to evaluate the safety profile, tolerability, and immunoregulatory (pharmacodynamic; PD) activity of panobinostat administered in combination with ipilimumab (anti-CTLA4 antibody) to subjects with unresectable Stage III or Stage IV melanoma. We will test the hypothesis that panobinostat administered in combination with ipilimumab will be well tolerated and that the addition of panobinostat will augment the clinical efficacy of ipilimumab.

1.3 Objectives

Primary Objective:

- To define the safety, tolerability, dose-limiting toxicities (DLTs), maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of panobinostat administered in combination with ipilimumab in subjects with unresectable Stage III or Stage IV melanoma

Secondary Objectives:

- To describe the preliminary anti-tumor activity of panobinostat administered in combination with ipilimumab to subjects with unresectable Stage III or Stage IV melanoma
- To evaluate the pharmacodynamic (PD) effect of the combination regimen on biomarkers in peripheral blood samples and tumor biopsy specimens

Exploratory Objectives:

- To explore potential relationships between panobinostat exposure, biomarker measures, anti-tumor activity, and adverse event, for each combination dose regimen

1.4 Background

1.4.1 Summary of Results from Panobinostat Investigational Program

Panobinostat (LBH589) belongs to a structurally novel cinnamic hydroxamic acid class of compounds and is a pan-inhibitor of Class I, II and IV histone deacetylases (HDACs). HDACs are involved in the deacetylation of histone and non-histone cellular proteins, targeting lysine groups on chromatin and transcription factors and various non-histone proteins such as p53, tubulin, heat shock protein 90 (Hsp90), and retinoblastoma protein (Rb). In addition to modulation of the acetylation state and function of histones, treatment of tumor cells with Panobinostat also resulted in increased acetylation of cytoplasmic proteins, including Hsp90, a target of HDAC6 and a major chaperone protein required for the stabilization of many key proteins implicated in cancer development and growth onco-proteins. Panobinostat-induced acetylation of Hsp90 inhibited the protein-stabilizing function of Hsp90 and led to the destabilization and resulting degradation of anti-tumor targets, such as break point cluster region-abelson (BCR-abl, HER2/neu, estrogen receptor, androgen receptor, and anti- apoptotic proteins such as phospho-AKT, JAK-2 ^{V617F}, pJAK-2. Consequently, cells which exhibited high *in vitro* sensitivity to Panobinostat include those cultured from tumors known to be driven by the aforementioned onco-proteins. Panobinostat treatment of the HER+-driven BT474 breast cancer cell line resulted in increased acetylation

of Hsp90 and depletion of Hsp90 client onco-proteins. As a further illustration of the effect of Panobinostat on Hsp90 client proteins, Panobinostat treatment of CML cell lines or primary blasts cells derived from patients in CML blast crisis resulted in the degradation of wild type and mutant BCR-abl, including the T3151 BCR-abl mutant resistant to inhibition by all tyrosine kinase inhibitors (TKIs) currently approved for the treatment of CML. Consistent with its pan-HDAC inhibition in HL (Hodgkin's lymphoma) cell lines, Panobinostat treatment resulted in effects on levels of JAK/STAT signaling proteins in all tested HL cell lines. HL is a disease model characterized by aberrant activation of signaling pathways, including constitutive activation of several components of the JAK/STAT pathway. Panobinostat treatment increased the expression of STAT1 and decreased the expression of both total STAT6 and activated phospho-STAT6; both effects are known to be interrelated and to correlate with tumor cell death. These results indicated that Panobinostat modulated the JAK/STAT pathway in a manner that was consistent with reversing effects associated with HL cell survival leading to apoptosis. Panobinostat has shown antitumor activity in preclinical models and cancer patients and has been formulated as an oral capsule and a solution for intravenous (i.v.) injection. Both the oral and i.v. formulations are currently being investigated in Phase IB/II studies in advanced solid tumors and hematological malignancies. Two Phase III studies with oral Panobinostat are ongoing in relapsed/refractory multiple myeloma (MM) and in post-transplant Hodgkin's lymphoma (HL) patients in complete remission who are at high risk for relapse.

1.4.1.1 Preclinical pharmacology

The drug was devised through iterative design and combinatorial approaches, and has shown inhibitory activity on purified total cellular HDAC and on most HDAC isoforms in nanomolar concentrations. It induced expression of cell-cycle control genes including CDKNIA (p21) and inhibited proliferation of a variety of tumor cell lines at low nanomolar concentrations. panobinostatt has demonstrated differential toxicity for tumor cells versus normal cells and has shown anti-tumor activity in cultured tumor cells which was associated with persistent HDAC inhibition, including melanoma cell lines. The drug exhibited differential antiproliferative activity against a broad range of solid tumors cell lines and high sensitivity in lymphomas and hematologic malignancies cell lines, including acute myeloid leukemia (AML) and MM, and induced consistent tumor growth control in various tumor-bearing xenografted mice and increased histone-H3 and -H4 acetylation in excised tumors. Panobinostat has shown synergistic or additive anti-tumor effects in combination with other anti-cancer agents such as trastuzumab, docetaxel, bortezomib or standard cytotoxic agents e.g., doxorubicin, fludarabine, Ara-C in murine xenograft and human in vitro models.

1.4.1.2 Animal pharmacokinetics and drug metabolism

The absolute oral bioavailability of panobinostat is ~50% in dogs, ~6 to 22% in rat, and 2.4% in rabbits. It has moderate plasma protein binding that is independent of plasma concentrations. Its *in vivo* metabolism in dogs, rabbits and rats involves biotransformation reactions including reduction, oxidation, hydrolysis, with glucuronidation found only in rats. Panobinostat is a potent inhibitor of CYP2D6 *in vitro*, but weak inhibitor *in vivo* (clinical increase of dextromethorphan AUC of 1.6-fold). It shows a weak time-dependent inhibition of CYP3A *in vitro*. Based upon drug-interaction modeling, Panobiostat is not expected to clinically interact with sensitive CYP3A substrates

CYP3A4 appears to be the main enzyme involved in the oxidative metabolism of

panobinostat, (70-98% in human liver microsomes). Clinically, metabolism by CYP3A contributes to only ~40% of total panobinostat clearance as determined from the magnitude of drug interaction elicited with ketoconazole.

1.4.1.3 Non-clinical safety and toxicology

Panobinostat has shown genotoxic potential in bacterial and eukaryotic systems. It has a preclinical signal for QT prolongation based on *in vitro* electrophysiological investigations and *in vivo* studies using telemeterized dogs. In the oral repeated doses toxicology studies, the primary target organs were identified as the erythropoietic, myelopoietic, and lymphatic system. Other secondary target organs included the gastrointestinal (GI) tract, reproductive system, thyroid and bone. Evidence of reversibility was observed for all white blood cells.

Oral administration of panobinostat to rats and rabbits is associated with embryo-fetal toxicity (increased resorptions/decreased live litters). Although no major malformations were observed, the incidence of fetal skeletal variations and anomalies was increased. Based upon the results of preclinical studies, hematology parameters, thyroid function and cardiac function assessments have been included in clinical trials. Panobinostat poses a reproductive risk to men and women of child bearing potential; therefore use of adequate birth control methods is required while a patient is on drug and for 12 weeks after the last dose.

1.4.1.4 Human pharmacokinetics and Safety

In humans, panobinostat exhibits a linear PK profile following i.v. administration. panobinostat exposure is nearly dose- proportional at doses below 60 mg following oral administration; inter-patient variability in exposure (AUC) is 60% with oral and 40% with i.v. panobinostat (coefficient of variability [CV]). The drug has a rapid oral absorption Tmax = 1 hour. Absolute bioavailability is 30% and elimination t1/2 is approximately 15 hours.

The clinical development of panobinostat has been conducted with both an i.v. and oral formulation [19-24] The major dose-limiting-toxicity (DLT) for both formulations administered as a single agent is reversible thrombocytopenia. For the i.v. formulation, a weekly i.v. dosing scheme (Day 1, Day 8 every 21 days) is currently used in clinical studies with thrombocytopenia being managed by dose and schedule adjustment. For the oral formulation, a pooled analysis of data from phase I/II studies indicates that thrombocytopenia is the most common lab abnormality of any grade and of Grade 3-4 in patients treated with the three-times-a-week (TIW), every week (QW) and every-other-week (QOW) schedules. The median time to Grade 3 thrombocytopenia appears to be shorter with the QW dosing as compared with the QOW dosing. The magnitude of platelet count decline is dose-dependent and related to the baseline platelet count. The median time to recovery from severe thrombocytopenia, Grade 3-4 to Grade 2 or below, is approximately 8 days for doses up to 40 mg in solid tumors and lymphomas. The median time to recovery from severe thrombocytopenia is much longer (up to approximately 74 days) for doses up to 60 mg used in hematologic malignancies. Preliminary evidence in patients with solid tumors and lymphomas suggests that switching from the QW to the QOW schedule may be more effective than other dose modifications for reducing the recurrence of thrombocytopenic events

QT prolongation, a known class effect of HDAC inhibitors, appears to be formulation, dose and schedule dependent. For the i.v. formulation, QTcF prolongation of clinical relevance (Grade ≥3 with absolute increase >500 msec) was seen in 4/15 patients (26.7%)

treated with panobinostat daily x 7, in 2/29 patients (6.8%) treated with the daily x 3 schedule (1 Grade 3 and 1 Grade 4 torsade de pointes) and in 2/56 (3.6%) patients treated with the weekly dosing schemes. With the "intermittent" oral dosing (TIW QW and TIW QOW) used in clinical trials, QTcF >500 msec is uncommon (6/635 patients, 0.9%) and noted only with the oral QW schedule. The mean QTc changes from baseline across all oral doses and schedules have been limited to <10 msec and observed during the first week of cycle 1 treatment. These changes did not coincide with the maximum concentration/time profile of the drug in plasma. No torsade de pointes has been reported in clinical trials with intermittent i.v. or oral dosing regimens

Asymptomatic T-wave abnormalities including inverted T-waves, flat T-waves, and biphasic T-waves are the most common ECG abnormalities reported to date with panobinostat. Asymptomatic sinus tachycardia has also been noted in approximately 40% of patients who received i.v. or oral panobinostat

Other common toxicities included fatigue (dose-related, but Grade 3-4 limited with both oral schedules), nausea, vomiting and diarrhea (more common with oral, and mostly Grade 1-2, regardless of the schedule; manageable with loperamide). Based on these preclinical and clinical observations, the safety and efficacy of panobinostat as a single agent and in combination with other chemotherapeutic agents is being explored in multiple Phase IB, II and III studies in patients with solid tumors and hematologic malignancies.

1.4.2 Summary of Results from Ipilimumab Investigational Program

Enhancement of the magnitude and potency of tumor antigen-specific adaptive cellular responses by T cells continues to be a major goal for cancer immumotherapy. Full activation of naive T cells requires not only stimulation of antigen receptor by peptide/major histocompatibility complexes, but also by costimulatory signals. [29] These signals are provided by the engagement of CD28, which is constitutively expressed on T- cell surface, with CD80 and CD86 molecules which are present on antigen presenting cells (APC). CD28-B7 costimulatory signals are critical for the induction of T-cell proliferation, cytokine secretion, and effector functions which ultimately translate into clinical effects.[30] CTLA-4 is an activation-induced T-cell surface molecule that binds CD80 and CD86with greater avidity than CD28. CTLA-4 ligation down regulates T-cell responses, which results in an abrogation of the clinical effects provided by T-cell activation.[32] Blockade of CTLA-4/B7 interactions results in an increase in T-cell activation.

1.4.2.1 Nonclinical Pharmacology

Ipilimumab is a fully human immunoglobulin G (IgG1)κ anti-CTLA-4 monoclonal antibody (mAb). In vitro studies were performed with ipilimumab to demonstrate that it is specific for CTLA-4, actively inhibits CTLA-4 interactions with CD80 and CD86, does not show any cross-reactivity with human CD80, CD86 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, but the half life of ipilimumab is shortened by species-level differences in immunogenicity of the product protein. Ipilimumab was originally produced and purified from a hybridoma clone. Subsequently, a transfectoma (Chinese Hamster Ovary [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. Please see the current version of the Investigator Brochure.[26]

1.4.2.2 Clinical Safety

Safety data are available for more than 2900 subjects treated in 25 completed clinical trials in multiple tumor types at a range of ipilimumab doses between 0.3 mg/kg and 20 mg/kg [31-34]. Most experience with ipilimumab exists at the 3 mg/kg and 10 mg/kg dose levels. Subjects who received ipilimumab at 3 mg/kg were treated in clinical trials conducted early in the development program and received either a single or multiple injections. Intra-subject dose escalation indicated that subjects with no response at 3 mg/kg dose level may respond to 9 mg/kg. Ipilimumab doses of up to 10 mg/kg are currently being investigated for the treatment of melanoma and other tumor types. Nonetheless, in March 2011, ipilimumab at 3 mg/kg for 4 induction doses was approved by the FDA for metastatic melanoma. Drug-related adverse events (AE) were reported in studies with ipilimumab as monotherapy as well as in combination with vaccines, cytokines or chemotherapy. The AE profile of ipilimumab is relatively well characterized. Among subjects who received ipilimumab at 10 mg/kg (N = 658) treatment-related AEs were reported in 85.3% (561/658) of subjects. AEs of grade 3 or higher were reported in 31.2% (205/658) of subjects. Most frequently reported treatment-related AEs of any grade (reported in ≥ 10% of subjects who received ipilimumab at 10 mg/kg) included diarrhea, fatigue, rash, pruritus, nausea, pyrexia, vomiting, and colitis. Treatment-related AEs associated with the use of ipilimumab generally tend to be immune-mediated effects. These AEs, termed immune-related adverse events (irAEs) presumably represent the impact of CTLA-4 inhibition and immune modulation on normal tissue function. Drug-related Grade 3 or 4 SAEs in subjects who received ipilimumab 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. Please refer to the Package Insert (PI) for the latest update on SAEs.[29]

As of 30 Jun 2009, study-drug related deaths based on investigator's assessment were reported in approximately 1% (35/3800) of subjects treated with ipilimumab. Eleven of 35 study-drug related deaths were reported for subjects known to have received ipilimumab at 10 mg/kg multiple doses; 17 of the 35 related deaths were reported on studies that are ongoing and remain blinded to treatment. While a causal role of ipilimumab in these 35 deaths could not be ruled out, confounding factors were identified in most of these cases.

Immune-Related Adverse Events (irAEs)

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

Among the 658 subjects who received ipilimumab at 10 mg/kg, 73.4% (483/658) developed any grade irAEs which predominately involved the GI tract, endocrine glands, liver, or skin. GI irAEs of any grade were reported for 40.0% (263/658) of subjects, and grade 3-4 GI irAEs were reported for 12.6% (83/658) of subjects. Inflammatory hepatotoxicity of any grade was reported for 9.0% (59/658) of subjects, and grade 3-4 inflammatory hepatotoxicity was reported for 6.4% (42/658) of subjects. Endocrinopathy of any grade was reported for 7.6% (50/658) of subjects, and grade 3-4 endocrinopathy was reported for 2.4% (16/658) of subjects. With few exceptions these irAEs were clinically manageable and reversible with supportive care or corticosteroids. In responding subjects, addition of corticosteroids does not appear to have a temporal relationship to change in objective tumor response. Immune-related AEs associated with ipilimumab appear to be dose dependent. In the dose-ranging study, CA184022, overall incidence of irAEs increased with increasing ipilimumab doses of 0.3 to 10 mg/kg. Comparison of the 3 and 10 mg/kg dose groups also showed an increased overall frequency of grade 3-4 irAEs for the higher dose group (the difference was 18.4%). The overall safety profile for the 10 mg/kg ipilimumab was consistent with that of the 3 mg/kg ipilimumab. Please refer to the most updated PI. [29]

1.4.2.3 Clinical Efficacy

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. Early results show that ipilimumab is active in subjects with Stage IV malignant melanoma. The objective responses with ipilimumab have been observed across a spectrum of doses and schedules. Based on a preliminary analysis for study MDX010-15 involving ipilimumab 10 mg/kg multiple doses, approximately 34%of subjects (N = 23) were progression-free at 6 months and about 17% were progression-free at 1 year. In comparison, for study MDX010-08 involving ipilimumab 3 mg/kg multiple doses, about 11% subjects (N = 37) had progression-free at 6 months and about 6% at 1 year.

The results of a phase III randomized trial of ipilimumab alone at 3 mg/kg or with a peptide vaccine compared with vaccine alone have been described, showing that ipilimumab significantly prolongs survival in previously treated patients with advanced melanoma compared to the control arm.[35] The median OS for patients receiving ipilimumab alone or with a peptide vaccine was 10.1 and 10.0 months, respectively, compared with 6.4 months for the vaccine-alone control arm (P = .003 and P < .001, and hazard ratios of 0.66 and 0.68, compared with vaccine alone). In that trial, the rate of grades 3-4 dose limiting side effects was 8.1%, with the majority of events being immune related adverse events (irAEs) related to the immune mechanism of action of ipilimumab. Predominant events were skin related, colitis, hypophysitis and hepatitis. Virtually all dose limiting and other toxicities were reversible with the use of systemic steroids or in rare cases the TNF blocking antibody Infliximab. Recently, the results of a large placebo-controlled phase III study in 502 patients treated with first-line DTIC with or without ipilimumab (10 mg/kg) were presented and published[10]. In that trial, survival was prolonged in the ipilimumab+DTIC containing arm compared to chemotherapy alone with p=0.0009 and a hazard ratio of 0.72 favoring ipilimumab+DTIC. Median survivals in that trial were 11.1 months for the ipilimumab arm versus 9.1 months for the control chemotherapy cohort. The results of these two trials led to the approval of ipilimumab for metastatic melanoma in March, 2011.

Consistent with the known mechanism of action of ipilimumab the reduction in tumor burden in melanoma studies was characterized by novel patterns of measurable clinical effect. In addition to objective response as measured by RECIST 1.1, novel patterns of clinical activity, which are related to the immunological mechanism of action of ipilimumab, were reported. These patterns were characterized by overall reductions from baseline in total tumor burden after the appearance of new lesions and/or after an initial tumor burden increase.

1.4.3 Rationale for Starting Doses of Panobinostat and Ipilimumab

Based on data from the nonclinical pharmacology studies and monotherapy panobinostat studies the TIW dose regimen is hypothesized to result in target inhibition of HDAC activity while maintaining an acceptable safety profile. Therefore, the TIW dose regimen of PANOBINOSTAT has been selected for this study. In the ongoing monotherapy study, the 10 and 20 mg TIW dose cohorts have demonstrated adequate safety and tolerability. In this study, PANOBINOSTAT will be administered as a formulated capsule that has been used in the clinic. The major toxicities of PANOBINOSTAT, being thrombocytopenia and cardiac in nature, do not overlap with the major known side effects of ipilimumab. Both 3 and 10 mg/kg doses of ipilimumab have been associated with anti-tumor activity in melanoma subjects. Based on the potential for better tolerability, the lower, 3 mg/kg, dose has been selected as the starting dose of ipilimumab for this study.

1.4.4 Rationale for Dose Escalation Phase I Design

The 3+3 design that is commonly used in Phase I oncology trials, though widely accepted and used mainly due to ease of implementation, has known limitations. These include a lack of statistical basis for dose escalation decisions and for determination of the MTD, i.e. the MTD is not based on a target toxicity probability, it typically underestimates the true MTD, and may allow patients to be treated at suboptimal doses. Prior information on the adverse event profile of ipilimumab at the higher studied dose of 10mg/kg based on 658 treated subjects reported a 31.2% toxicity rate for drug-related adverse events of grade 3 or above.[26] In addition previous data on panobinostat indicate a less than 5% toxicity rate for drug-related adverse events of grade 3 or above.[28] Whereas results from nonclinical studies suggest that synergistic/additive antitumor activity from combining ipilimumab with panobinostat may be seen in the clinic, potential benefit versus risks with this combination have not been evaluated in humans. In this first clinical study with the combination, therefore, it is reasonable to assume that the maximum acceptable ≥ Grade 3 toxicity rate at the MTD of the combination should not exceed the Grade 3 toxicity rate for ipilimumab (combination partner with a higher Grade 3 toxicity rate when administered as monotherapy). The target toxicity and the toxicity interval at the MTD will be 18% and 17-19%, respectively, and will be consistent with keeping the ipilimumab dose at 3 mg/kg for this dose escalation trial. These proposed target toxicity rates, with the tight interval is also consistent with the general principles of the widely used 3+3 dose escalation design in oncology studies. Based on the above, and the need to better monitor ongoing toxicities due to the potential risk of combined side effect, the modified TPI (mTPI) design[40] which uses Bayes rule under decision theoretic framework, was selected as an appropriate design for this study. The design provides more confidence in estimating the toxicity rate at each dose, selects the MTD based on a target toxicity probability, and it correctly identifies the true MTD more often than the 3+3 design, based on simulation results. The mTPI was selected among other Phase I oncology designs including Bayesian designs such as CRM, due to additional advantages of simplicity of

implementation and treating fewer subjects at suboptimal or at toxic doses.

1.4.5 Rationale for use of Immune-related Response Criteria (irRC) to Guide Clinical Care and Assessment of Clinical Activity

In prior ipilimumab clinical studies, particularly those in metastatic melanoma, clinical efficacy appears to be characterized by objective tumor response (CR and PR), durable stable disease (commonly lasting 6 or more months in subjects receiving 10 mg/kg ipilimumab), and stable disease evolving to objective response after more than a year of follow-up in the absence of alternative anti-cancer therapy. In addition, melanoma subjects receiving ipilimumab who are found to have new lesions at the first follow-up tumor assessment and who are therefore scored as progressors by the mWHO or RECIST criteria have been observed to have stable or decreasing tumor burden in spite of the presence of new lesions. Subjects with such "mixed responses" have been reported to go on to continued reduction in tumor burden in the absence of alternative anti-cancer therapy and objective tumor response by any measure.

The irRC were developed to provide a guide for clinical care of subjects on immunotherapy. Subjects with stable (irSD) or significantly decreasing (irPR) tumor burden despite the presence of new lesions remain on study and continue to receive study drug. Subjects with increasing tumor burden (irPD) are declared progressors and taken off study drug. To account for the various spectra of patterns of new lesions, measurable new lesions are added to the calculation of tumor burden (e.g. added to the SPD of the index lesions). Thus, subjects with many large new lesions will be scored as irPD even if the index lesions are stable or decreasing.

1.4.6 Rationale for use of Blood and Tumor Tissue Biomarkers

Previous ipilimumab studies explored in their main study design a variety of potential biomarkers in melanoma patients. Results from studies CA184004 and CA184007 suggested the possible biomarkers listed below for further research:

• An increase in peripheral-blood Absolute Lymphocyte Count (ALC) was associated with benefit (Best Overall Response of Complete Response, Partial Response, or prolonged Stable Disease (SD), i.e. SD lasting at least 24 weeks from first dose) and occurred in a dose-dependent fashion favoring 10 mg/kg ipilimumab. In addition to change in ALC over time, ALC value just prior to a third dose of ipilimumab also was associated with benefit.

We will also evaluate FOXP3 and IDO tumor tissue expression at baseline as predictive of clinical benefit, as well as flow cytometry of CD4 and CD8 T cells for Ki67, EOMES and ICOS, predictive markers that have been found to be associated with benefit using ipilimumab. Serum cytokine assays with a multiplex analysis for IL-6, IL-10 and gamma interferon will be conducted, as well as T cell intracellular staining for those cytokines and assessment of allo MLR reactivity as a marker of T cell integrity.

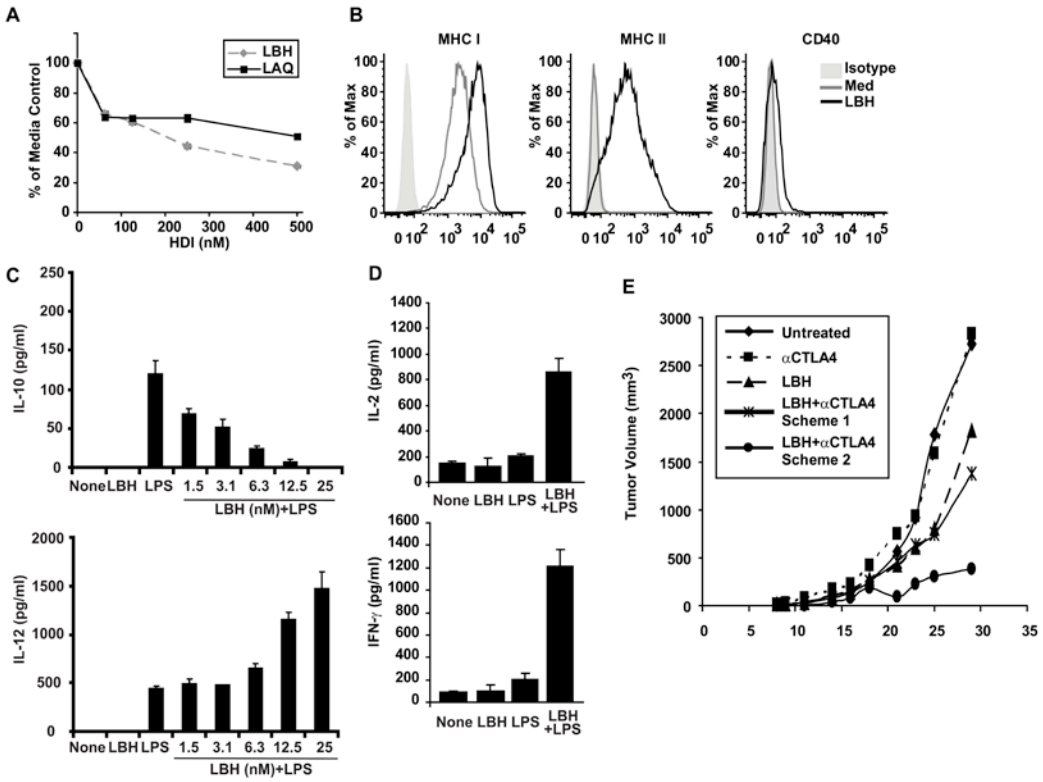
A mean increase in the percentage of activated (HLA-DR+), CD4+ and CD8+ T cells and central memory (CD45-RO and CCR9+) T-cells and a mean decrease in percent of naive CD4+ and CD8+ T-cells in Week 4 and Week 12 post-ipilimumab treatment samples has been observed in several studies. Based on these results, a biomarker plan is included in this trial which allows sample collection for biomarker analyses to determine the effects of PANOBINOSTAT on the immune-regulatory effects of ipilimumab treatment. Subjects will

be asked to give blood samples, serum and/or tumor tissue samples for predictive, pharmacodynamic and exploratory biomarker research.

1.5 Overall Risk/Benefit Assessment

Pan-HDIs have been shown to have antitumor activity both *in vitro* and *in vivo*. In addition to inducing cell cycle arrest and apoptosis of tumor cells, these compounds are also endowed with immunoregulatory properties. For instance, the pan-HDI TSA has been shown to up-regulate MHC and costimulatory molecules on melanoma cells, making them more susceptible to attack by IFN-γ secreting T-cells. In addition, Vo et al. have demonstrated that *in vivo* treatment of melanoma bearing mice with the hydroxamic acid analogue pan-HDI LAQ824, significantly augment the anti-melanoma activity of adoptively transferred antigen-specific T-cells[25]. Furthermore, studies in our lab have shown that LAQ824 inhibits the production of IL-10 in APCs rendering these cells more inflammatory and capable of effectively prime naïve antigen-specific $CD4^+$ T-cells and able of restoring the responsiveness of tolerant T-cells (Wang et al. *J Immunol.* 186(7): 3986-96, 2011

Panobinostat (LBH589) which is a potent cinnamic hydroxamic acid analog deacetylase inhibitor, induces apoptosis in multiple tumor cell lines *in vitro* at nanomolar concentrations. Panobinostat belongs to the same family of hydroxamic acid derivatives than LAQ824, but has the following advantages: ***(i)*** It is an oral agent, ***(ii)*** Clinical studies in humans have shown that panobinostat has a better safety profile than LAQ824 (which was removed from further clinical development due to cardiac toxicity) and, ***(iii)*** LBH displays more potent HDAC inhibition than LAQ824 both *in vitro* and *in vivo*. Indeed, recent studies in our lab have confirmed that LBH589 is more potent than LAQ824 in inhibiting the proliferation of B16 melanoma cells *in vitro* (**Fig. 1A).** Of note, panobinostat-treated B16 cells are rendered immunogenic due to their enhanced expression of MHC class I and II molecules and the costimulatory molecule CD40 (**Fig. 1B**). In addition to its effect upon melanoma cells, panobinostat also influences the inflammatory status of APCs since treatment of these cells resulted in a dose-dependent inhibition of IL-10 that is accompanied by increased production of the pro-inflammatory cytokine IL-12 (**Fig. 1C**). These inflammatory APCs are in turn, better activators of naïve antigen-specific $CD4^+$ T-cells *in vitro* (**Fig. 1D**).



The results above with LBH589 have been recently extended into human melanoma studies. First, *in vitro* treatment of several human melanoma cells, including BRAF WT (SKMEL21), BRAF mutants (WM983A, WM35 and WM164) or melanoma cells with constitutively activated STAT3 (WM793), with nanomolar doses of LBH589 resulted in a dose dependent inhibition in cell growth **(Fig. 2A).** Cell lines WM983, SKMEL21 and WM793 were the most sensitive to LBH589. Of note, normal melanocytes (HEMn-LP) were not affected by LBH589 at all the doses evaluated. Second, exposure of human melanoma cells to LBH589 resulted in cell cycle arrest in G1 **(Fig. 2B)** and induction of apoptosis **(Fig. 2C)** as demonstrated by increased cleaved PARP in LBH589-treated WM793 and WM983A cells. Third, treatment with LBH589 resulted in increased expression of MHC class I and the costimulatory molecules CD80, CD86 and CD40 in WM983A human melanoma cells **(Fig.2D).**

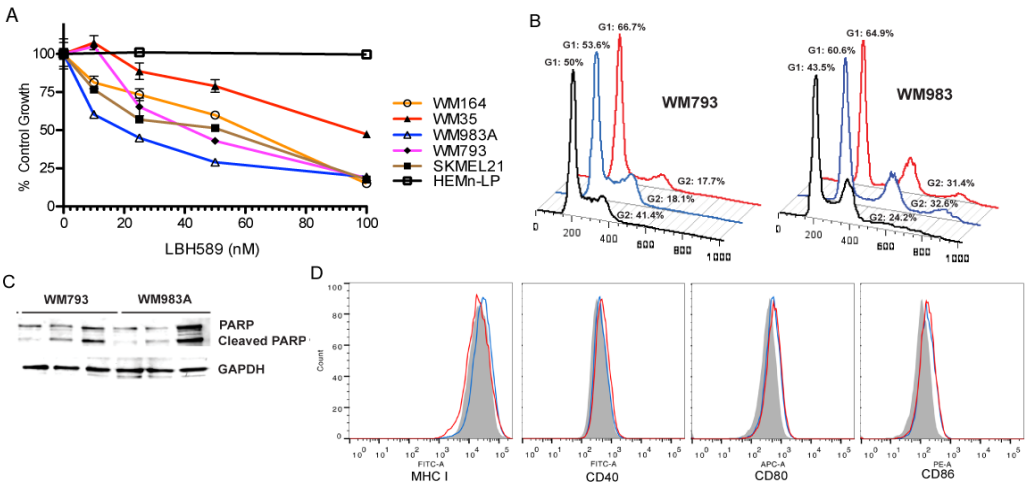


Figure 2. Effects of LBH589 in human melanoma cells. **(A)** Human melanoma cells were treated with the indicated concentrations of LBH589 for 48 hours and subject to an MTS cell proliferation assay. **(B)** Cell cycle analysis of fixed WM793 and WM983A human melanoma cells stained with propidium iodine. **(C)** LBH589 induced apoptosis of WM793 and WM983A as determined by cleaved PARP (**D)**WM983A cellswere treated with LBH for 48 hours and the expression of MHC class I, CD40, CD80 and CD86 were determined by flow cytometry using specific antibodies.

The immunomodulatory effects of panobinostat upon melanoma cells, APCs and T cells together with the demonstration by others that panobinostat inhibits STAT3, a transcriptional activator of IL-10, and induces changes in CCL22 that allow for Th1 polarization points to this HDI as a novel immune adjuvant with the potential to enhance the therapeutic efficacy of immune stimulating agents like anti-CTLA4 antibodies for the treatment of melanoma. Indeed, we recently treated B16 melanoma bearing mice with anti-CTLA4 antibodies alone, LBH589 alone or a combination thereof. The therapeutic regimen combining panobinostat and CTLA4 blockade significantly delayed melanoma growth *in vivo* as compared to either agent alone shown in **Fig 1E**.

Currently available treatment options for advanced melanoma including Ipilimumab and Vemurafenib, as well as high-dose interleukin-2, produce a spectrum of significant toxicities while providing meaningful clinical benefit. Demonstration of significant clinical responses and prolonged overall survival in subjects with advanced melanoma with the mutant selective inhibitor vemurafenib (PLX4032) has provided clinical validation for mutated B-RAF as a therapeutic target in this tumor type. Duration of response with this agent as monotherapy, however, appears to be limited. Ipilimumab is a potent immunomodulatory agent that has already demonstrated durable clinical benefit and benefit in overall survival in subjects with advanced melanoma. When considered together with the data on observed additive/synergistic anti-tumor activity and promotion of its immune effects in nonclinical studies and their distinct mechanisms of action, administration of panobinostat in combination with ipilimumab can provide a novel treatment regimen that could have the potential to provide significant sustained clinical benefit in this subject population. Potential benefits from this combination, therefore, outweigh the potential risks for toxicity. Assessment of safety and tolerability of panobinostat has been addressed in a monotherapy

study. In this study, panobinostat monotherapy has been administered to over 50 subjects, and continues to exhibit an acceptable tolerability profile that supports its further exploration. There is also preliminary evidence of clinical activity by way of subjects with advanced cancer continuing with panobinostat administration for prolonged periods of time. Principal AEs related to panobinostat administration in the clinic have comprised of constitutional symptoms including fatigue, nausea, diarrhea, vomiting, anorexia, skin rash and decreased appetite. These events are easily monitored by protocol defined clinical assessments (scheduled physical examinations, repeated vital sign measurements, and clinical laboratory assessments) and/or can be managed by supportive measures in conjunction with protocol-specified dose modifications. No eye disorders associated with changes in the retina or the optic nerve have been reported in the clinic to date, as was observed among individual animals at high doses in the nonclinical studies. Given the superficial nature of these lesions, this finding is not considered prohibitive to continued evaluation of panobinostat in the clinic. The most common adverse events with ipilimumab are inflammatory in nature, presumably related to the immune-based mechanism of action, correlated with clinical activity and nearly always reversible with medical management. The most frequently reported drug-related adverse events include diarrhea, colitis, endocrinopathies, hepatitis, and rash. There is potential for overlapping GI toxicity with the combination. Appropriate monitoring plan and guidance on early intervention and management of these events, as well as dose modification guidelines have been included in the protocol. In order to minimize the overall risks to participating subjects, this protocol has inclusion-exclusion criteria appropriate to the population and proposed dosing regimens, exclusionary screening tests, and specific follow-up safety assessments. Based on the potential adverse event profile, appropriate clinical, laboratory, and management algorithms have been incorporated into the protocol. The adverse events (AEs) and serious adverse events (SAEs) will be reviewed on an ongoing basis by the PI and the clinical research team and will be reviewed periodically with an independent DMC to look for trends and any safety issues. Since both PANOBINOSTAT and ipilimumab are experimental agents, it is possible that unforeseen, unknown, or unanticipated reactions can occur during the study.

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50). The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

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

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, written and dated approval from the IRB/IEC will be obtained for the protocol, consent form, subject recruitment materials/process (eg, advertisements), and any other written information to be provided to subjects. The investigator will also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information and any updates.

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

2.3 Informed Consent

Investigators will ensure that subjects, or, in those situations where consent cannot be given by subjects, their legally acceptable representatives, are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate. The informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is a Phase 1 open label study of panobinostat administered in combination with ipilimumab. Subjects with unresectable Stage III or Stage IV melanoma who meet the eligibility criteria will undergo screening evaluations within 28 days prior to initiation of study therapy. The study will consist of a dose escalation assessment of the safety and tolerability of oral panobinostat administered concurrently in combination with ipilimumab. Treatment will be divided into induction with ipilimumab and panobinostat and a maintenance phase with panobinostat alone consistent with the general principles of ipilimumab therapy. It is anticipated that this evaluation will enable selection of the RP2D of this combination for further clinical testing. A study schematic is presented below:

Each treatment cycle will be 42 days (6 weeks) during the induction phase, and 84 days (12 weeks) during the maintenance phase. Panobinostat will be administered orally TIW on Days 1-42 of each 42 day treatment cycle. Ipilimumab will be administered intravenously (IV) once every 3 weeks on Days 1 and 22 of each treatment cycle. The induction phase will last for up to 2 treatment cycles. During the maintenance phase, panobinostat will be administered orally TIW on Days 1-84 of each 84 day treatment cycle. Subjects will continue maintenance panobinostat treatment with their designated combination dose regimen until progression of disease, discontinuation due to toxicity, withdrawal of consent or any other reason as specified in Section 3.4.

Table 3.1 Dose Escalation regimen for Panobinostat and Ipilimumab

Dose Cohort	Panobinostat Dose	Ipilimumab Dose
1	5 mg po TIW	3 mg/kg
2	10 mg po TIW	3 mg/kg
3	15 mg po TIW	3 mg/kg
4	20 mg po TIW	3 mg/kg
-1	5 mg po TIW	1 mg/kg

Dose escalation: Subjects will be enrolled in successive cohorts of 3. An initial cohort of 3 subjects will be enrolled at the given dose level, and additional cohorts of 3 subjects may be added to the same dose level (e.g. increasing the total number of enrolled subjects from 3 to 6, 9 or 12) based on a modified version of a toxicity probability interval (TPI) design introduced by Ji et al.[40] The modified TPI (mTPI) design uses Bayes rule in a decision theoretic framework to determine the MTD based on a target toxicity (eg, dose limiting toxicity; DLT) probability p_T. A fixed number of subjects, 36, will be used during this dose escalation study. As the dose escalation proceeds under this design, the number of subjects enrolled at a given dose level depends on the number of the toxicities observed at that dose such that multiple cohorts of 3 subjects each may be enrolled to enable a dose escalation decision. The MTD is selected at the end of dose escalation as the dose with an observed toxicity rate closest to the pre-specified target toxicity probability P_T. In this study, an 18% target toxicity (P_T) is used. Background rationale as basis for selection of this target toxicity has been previously outlined in Section 1.4.6. Dose escalation will evaluate panobinostat at doses ranging from 5 to 20 mg TIW administered in combination with ipilimumab at a dose of 3 mg/kg. The first cohort will receive panobinostat orally at a dose of 5 mg PO TIW; ipilimumab will be administered IV at a dose of 3 mg/kg. Enrollment of successive cohorts of subjects will proceed with administration of escalating doses of panobinostat in combination with ipilimumab. Additional dose levels of panobinostat beyond the 20 mg PO TIW dose cohort may be added if appropriate based on the safety and tolerability profile of the combination, and after consultation and agreement between Investigators and Novartis. It is expected that all subsequent dose levels of panobinostat will be no more than 33% higher than the preceding dose. If the first dose cohort is demonstrated to have unacceptable toxicity, dose level -1 will be instituted with 5 mg PO TIW of panobinostat and ipilimumab at 1 mg/kg.

There will be no intra-subject dose escalation. Decisions regarding dose escalation between cohorts will be guided by the incidence of drug-related dose limiting toxicities (DLTs) occurring within 84 days (12 weeks; through Day 42 of induction cycle 2) of initiation of study therapy. If three patients complete their 84 day period of treatment without DLT, then at least three additional patients must exceed 9 weeks without MTD being reached to be able to dose escalate. This DLT observation interval is based upon inclusion of the known median times to onset of common immune-related adverse events attributed to ipilimumab (see Section 4.3.5.1) and allows for a substantial amount of time for unexpected toxicities with the combined administration of panobinostat and ipilimumab to emerge. Subjects who do not complete the DLT observation period for reasons other than drug-related toxicity will be replaced. One of the following five decisions will be made at the end of the DLT period for each cohort of 3 subjects based on the number of DLT's observed:

S: stay at the same dose and enroll a cohort of 3 more subjects at that dose
E: escalate to the next higher dose by enrolling 3 more subjects
D: de-escalate to the lower dose, and enroll 3 more subjects at the lower dose, or
DU: declare the current dose as unacceptable and unsafe, de-escalate to the lower dose, and enroll 3 more subjects at the lower dose
C: Study completed and dose is declared to be the MTD

Decisions S or E are allowed by the design if determined that the corresponding doses are safe based on the target toxicity. Decisions D or U are based on evidence of exceeding predetermined toxicity. With a target toxicity rate of 18%, allowing any dose with estimated P_T in the (17%, 19%) interval to be selected as the MTD in this study, and with a maximum fixed total of 36 subjects at the dose escalation phase in each arm, the algorithm for dose escalation decisions based on possible total number of subjects at each dose cohort is described in Table 3.2 below.

Table 3.2 **Dose Escalation Algorithm for each arm: modified TPI design**

Dose Escalation: This is a Phase I dose escalation trial and the sample size at each dose depends on the observed toxicity, and a total of 36 subjects at the dose-escalation phase allows sufficient number of subjects if needed, e.g. more than 6 subjects if dose-limiting toxicities are observed among 2 of 6 subjects, to better estimate the toxicity rates per dose, and more accurately determine the MTD. Cohorts of 3 subjects with possible expansions to 6, 9, or 12 subjects will be treated at each suggested dose level until MTD is defined.

In this protocol, we will be using a new phase I trial approach (Table 3.2), modified from a design from Ji et al[43]. This approach provides a broader phase I experience than the traditional 3+3 design, thus allowing for a more robust choice of an MTD. While setting the target toxicity rate at 18%, this design allows further examination of a dose when 2 DLTs occur among 6 patients, while still keeping the observed toxicity at the MTD well managed (it is below 26% for sample sizes ≥ 9). Moreover the MTD will exploit the isotonic nature of dose escalation in determination of the MTD.

Table 3.2 Decision Rules on dose escalation based on number of DLTs**

N*	Observed DLTs per cohort and treatment decisions												
		0		1		2		3		4		5		6
3		E		S		DU		DU	-	-	-	-	-	-
6		E		E		S		DU		DU		DU		DU
9		E		E		S		D		DU		DU		DU
12		E		E		E		C		DU		DU		DU

N* =number of subjects treated at a given dose level
S: stay at the same dose and enroll a cohort of 3 more subjects at that dose
E: escalate to the next higher dose by enrolling 3 more subjects
D: de-escalate to the lower dose, and enroll 3 more subjects at the lower dose, or
DU: declare the current dose as unacceptable and unsafe, de-escalate to the lower dose, and enroll 3 more subjects at the lower dose
C: Study completed and dose is declared to be the MTD

**for MTD target toxicity pT=18%, and allowing any dose with pT in (17%, 19%) to be selected
The modifications involve escalating the dose whenever the observed toxicity rate is below 17% and using the N-1st patient to define the change when the toxicity rate exceeds 19% and $N \geq 9$ to account for the fact that the design is being used in cohorts of 3 rather than continuously as

designed by Ji et al[43].

Based on the above design, escalation to the next higher dose level can occur if DLT's are observed in 0 of 3 or 6 subjects, in up to 1 of 6 subjects, in up to 2 of 12 subjects, and so on. If DLTs are observed in a greater number of subjects and escalation is not yet permitted, additional subjects in cohorts of 3 will be enrolled at the same dose in order to better estimate the true DLT rate at that dose until either escalation is allowed, the dose is deemed unacceptable and should not be used, or de-escalation is recommended, based on Table 3.2. All available clinical and laboratory data, and the nature, time of onset and time to resolution of DLTs observed during dose escalation will be reviewed to determine whether an alternate dose schedule should be examined after consultation between the Principal Investigator and the Data Monitoring Committee (DMC) if needed. If agreed upon, the alternate schedule will be identified by a protocol amendment and the MTD determined for the revised dose schedule.

This phase I study design has tended to be applied to a fixed sample size of 30. Due to the increased complexity of this combination-dose trial, we have chosen a sample size of 36.

3.2 Study Population

The study population consists of ipilimumab naïve subjects with unresectable Stage III or Stage IV melanoma who satisfy the inclusion and exclusion criteria.
For entry into the study, the following criteria MUST be met. No exceptions will be granted.

3.2.1 Inclusion Criteria

1) Signed Written Informed Consent

The signed informed consent form prior to the performance of any study related procedures that are not considered part of standard of care.

2) Target Population

a) Subjects who are ipilimumab naïve with progressive unresectable Stage III or Stage IV melanoma who are either treatment naïve or may have been treated with up to 3 prior treatments for melanoma (eg, chemotherapy, biologic or targeted therapy or IL-2).
b) Histologic or cytologic confirmation of stage III or stage IV melanoma
c) Measurable disease at baseline as assessed by CT and/or MRI
d) Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
e) Screening laboratory values must meet the following criteria
   i) WBCs $\geq 2000/\mu L$
   ii) Neutrophils $\geq 1500/\mu L$
   iii) Platelets $\geq 100 \times 10^3/\mu L$
   iv) Hemoglobin ≥ 9.0 g/dL
   v) Creatinine Serum creatinine ≤ 1.5 x ULN or creatinine clearance > 40 mL/minute (using Cockcroft/Gault formula)
   vi) AST ≤ 3 x ULN
   vii) ALT ≤ 3 x ULN
   viii) Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome who must have total bilirubin < 3.0 mg/dL)

3) Age and Reproductive Status

Men and women ≥ 18 years old

a) Men and women of childbearing potential (WOCBP) must be using an acceptable method of contraception to avoid pregnancy throughout the study and for at least 12 weeks after the last dose of investigational product in such a manner that the risk of pregnancy is minimized. See Section 3.3.3 for the definition of WOCBP.

b) Women must have a negative serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to the start of investigational product.

3.2.2 Exclusion Criteria

1) Target Disease Exceptions

a) Subjects with known or suspected brain metastasis, or brain as the only site of disease are excluded with the following exceptions.

i) Subjects with controlled brain metastasis (no radiographic progression at least 4 weeks following radiation and/or surgical treatment, off steroids for at least 4 weeks, and have no new or progressing neurological signs or symptoms) will be allowed.

b) Subjects with a history of prior malignancy with the exception of carcinoma in situ of the cervix or other malignancy diagnosed > 2 years ago that has undergone potentially curative therapy with no evidence of disease for the last ≥ 2 years and that is deemed by the investigator to be at a low risk of recurrence.

2) Medical History and Concurrent Diseases

a) Active autoimmune disease or a history of known or suspected autoimmune disease with the exception of subjects with isolated vitiligo, treated thyroiditis or resolved childhood asthma/atopy.
b) Known human immunodeficiency virus (HIV), active hepatitis A, or hepatitis B or C infection.
c) History of any hepatitis (eg, alcohol or non-alcohol steatohepatitis (NASH), drug-related, autoimmune)
d) Evidence of active infection that requires anti-bacterial, anti-viral, or anti-fungal therapy ≤ 7 days prior to initiation of study drug therapy
e) History of acute diverticulitis, or current chronic diarrhea
f) Active peptic ulcer disease even if asymptomatic
g) History of adrenal insufficiency (including subjects using replacement therapy)
h) Prior organ allograft or allogenic bone marrow transplantation
i) Uncontrolled or significant cardiovascular disease including, but not limited to, any of the following:
    i. Myocardial infarction within the past 6 months
    ii. Uncontrolled angina within the past 6 months
    iii) Any history of clinically significant ventricular arrhythmias (such as ventricular tachycardia, ventricular fibrillation or Torsades de pointes). Controlled atrial fibrillation by itself is not an exclusion criterion.
    iv) Baseline QTc interval greater than 500 milliseconds
j) Baseline toxicities from prior anti-cancer treatments > Grade 1.
k) Inability to be venipunctured and/or tolerate venous access.
l) Any major surgery within 4 weeks or a diagnostic procedure (eg incision, needle

biopsy) within 1 day of study drug administration.

m) Any current or recent (within 3 months) gastrointestinal disease that could potentially impact the ability to swallow and/or absorb study drug (ie, gastrointestinal surgery, malabsorption syndrome).
n) Diabetes mellitus uncontrolled by medication.
o) Known drug or alcohol abuse.
p) Presence of underlying medical condition that in the opinion of the Investigator or Sponsor could adversely affect the ability of the subject to comply with or tolerate study procedures and/or study therapy, or confound the ability to interpret the tolerability of combined administration of panobinostat and ipilimumab in treated subjects.

3) Allergies and Adverse Drug Reaction

a) History of allergy to components of ipilimumab or panobinostat, or known allergy to other antibody therapies.

4) Sex and Reproductive Status

a) WOCBP who are **unwilling or unable** to use an acceptable method to minimize the risk of pregnancy for the entire study period and for at least 12 weeks after the last dose of investigational product.
b) Women who are pregnant or breastfeeding.
c) Women with a positive pregnancy test on enrollment or prior to investigational product administration.
d) Sexually active fertile men not using effective birth control if their partners are WOCBP.

5) **Prohibited Prior Treatments and/or Therapies**

a) Exposure to any investigational drug within 4 weeks of study drug administration.
b) Any anti-cancer therapy (eg, chemotherapy, biologics, radiotherapy, or hormonal treatment) within 4 weeks or at least 5 half-lives (whichever is longer) of study drug administration.
c) Prior therapy with an anti-CTLA4 antibody or an HDAC inhibitor
d) Concurrent chemotherapy, hormonal therapy, immunotherapy regimens, or radiation therapy, standard or investigational.

6) **Other Exclusion Criteria**

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

3.2.3 Women of Childbearing Potential

Women of childbearing potential include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Post menopause is defined as:

• Amenorrhea ≥ 12 consecutive months without another cause and a documented serum follicle stimulating hormone (FSH) level >35 mIU/mL
• Women with irregular menstrual periods and a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL

- Women on hormone replacement therapy (HRT)

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

3.3 Concomitant Treatments

Medications taken within 4 weeks prior to study drug administration and while on study treatment must be recorded.

3.3.1 Prohibited and/or Restricted Concomitant Treatments

Restrictions on medications taken prior to enrollment in the study are described above in Section 3.3.2. Use of prescription and over-the counter medications (except medications from categories outlined below) is permitted at the discretion of the Investigator and must be recorded.

Concurrent use of the following medications or drug classes while on study therapy is prohibited. In the setting where eligible subjects are already taking these therapies, they should be switched to and stabilized on alternative medications as clinically indicated, and a minimum wash out interval of 5 half-lives of the prohibited medications should be allowed prior to initiation of study therapy.

1) Systemic or inhalational corticosteriods. Ocular use of corticosteriods is permitted as is the transient use of topical corticosteriods over a limited surface area. Replacement corticosteroids may be used up to the equivalent of 10 mg of prednisone daily.

2) Other immunosuppressive agents

3.3.2 Other Restrictions and Precautions

Panobinostat may also interact with and inhibit the metabolizing enzyme cytochrome P450 3A4. Therefore, strong inducers, inhibitors, or substrates of CYP3A4, should be used with caution during the study. Investigators are encouraged to consult the sponsor prior to the use of strong modulators of CYP450 activity. Appendix 2 provides examples of drugs in this category.

3.4 Discontinuation of Subjects from Treatment

Subjects MUST discontinue investigational products (and noninvestigational product at the discretion of the investigator) for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy (see Section 6.4)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Subject's inability to comply with the protocol

• Toxicity requiring discontinuation as outlined in the Guidelines for Dose Modification (Section 4.3.5)

All subjects who discontinue should comply with protocol specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).
If a subject was withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate case report form (CRF) page.

4 TREATMENTS

All protocol-specified investigational and non-investigational products are considered study drug.

4.1 Study Treatments

Study drug therapy will be divided into induction and maintenance phases. For the purpose of managing study visits and procedures, a treatment cycle will be defined as 42 days during the induction phase, and as 84 days during the maintenance phase.

4.1.1 Investigational Product

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations. In this protocol, investigational product(s) is/are: Panobinostat 5 mg, 10 mg, 15 mg and 20 mg capsules and Ipilimumab.

4.1.1.1 Ipilimumab (BMS-734016)

Study drug is to be administered and prepared according to the package insert as described below.

Preparation of Solution

- Allow the vials to stand at room temperature for approximately 5 minutes prior to preparation of infusion.
- Withdraw the required volume of YERVOY and transfer into an intravenous bag.
- Dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare a diluted solution with a final concentration ranging from 1 mg/mL to 2 mg/mL. Mix diluted solution by gentle inversion.
- Store the diluted solution for no more than 24 hours under refrigeration (2°C to 8°C, 36°F to 46°F) or at room temperature (20°C to 25°C, 68°F to 77°F).
- Discard partially used vials or empty vials of YERVOY.

Administration Instructions

- Do not mix YERVOY with, or administer as an infusion with, other medicinal products.
- Flush the intravenous line with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP after each dose.
- Administer diluted solution over 90 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding in-line filter.

Dose, Volume and Rate Calculations

Total dose should be calculated as follows:
Subject body weight in kg x 3 mg = total dose, mg
Total infusion volume should be calculated as follows: Total dose in mg divided by 5 mg/mL = infusion volume, mL

Rate of infusion should be calculated as follows: Infusion volume in mL divided by 90 minutes = rate of infusion, mL/min

For example, a subject weighing 114 kg (250 lb) and designated to receive ipilimumab at a dose of 3 mg/kg would be administered 342 mg of ipilimumab (114 kg x 3 mg/kg = 342 mg) with an infusion volume of 70 mL (342 mg divided by 5 mg/mL = 70 mL) at a rate of approximately 0.77 mL/min (70 mL divided by 90 minutes) in 90 minutes.

Ipilimumab (BMS-734016) Injection (5 mg/ml), must be stored refrigerated (2 - 8°C) with protection from light. Ipilimumab may be stored (5 mg/ml) in DEHP free IV infusion bags for up to 24 hours at room temperature or refrigerated (2°C - 8°C). This would include any time in transit and the total time for infusion. Drug must be completely delivered to the subject within 24 hours of preparation.

4.1.1.2 PANOBINOSTAT (LBH-589)

The drug product will be provided by Novartis and is an immediate-release solid oral dosage form capsule. The hard gelatin capsules contain the active substance Panobinostat lactate salt at dosage strengths of 5 mg, 10 mg, 15 mg and 20 mg as anhydrous free base. The inactive ingredients are: mannitol, microcrystalline cellulose, pregelatinized starch and magnesium stearate. An aqueous granulation and blending process produces the capsule content. The 5 mg, 10 mg, 15 mg, and 20 mg capsules are packaged in high-density polyethylene (HDPE) bottles with an induction seal and plastic CR closure. The current storage condition for all capsules strengths is: Do not store above 25°C. The retest date for the capsule formulations will be assigned based on available stability data.

4.1.2 Handling and Dispensing

The investigational pharmacist will ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the package insert. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor immediately.

Panobinostat 5 mg, 10 mg, 15 mg and 20 mg capsules must be stored below 25°C, in very tight packaging with water permeation <0.5 mg/day/liter, protected from light. Ipilimumab

(BMS-734016) Injection (5 mg/ml), must be stored refrigerated (2 - 8°C) with protection from light. Ipilimumab may be stored (5 mg/ml) in DEHP free IV infusion bags for up to 24 hours at room temperature or refrigerated (2°C - 8°C). This would include any time in transit and the total time for infusion. Drug must be completely delivered to the subject within 24 hours of preparation.

4.2 Method of Assigning Subject Identification

This is an open-label study. All enrolled subjects will be assigned a subject number, starting with 00001. After it has been determined that the subject meets all eligibility criteria, the investigator (or designee) will register the subject by following the enrollment procedures established at Moffitt. The following information is required for registration:

- Date of birth
- Gender
- Diagnosis
- Date of informed consent
- Planned date of 1st dose

The subject number will be assigned once the subject signs informed consent. Subject numbers will be assigned in the order of enrollment within 3 days prior to Day 1 of Cycle 1 dosing. Subjects who do not complete the DLT observation period for reasons other than drug- related toxicity will be replaced. Replacement subjects will receive the same treatment but will be assigned a new subject number.

4.3 Selection and Timing of Dose for Each Subject

As described under Study Design (Section 3.1), panobinostat will be administered orally concurrently in combination with intravenous ipilimumab. For each arm, treatment will be divided into induction and maintenance phases.

4.3.1 Study Treatments During Dose Escalation

Subjects will be enrolled in successive cohorts of 3. An initial cohort of 3 subjects will be enrolled at a given dose level, and additional cohorts of at least 3 subjects will be added based on the design as outlined in Section 3.1. The first cohort will receive panobinostat orally at a dose of 5 mg PO TIW; ipilimumab will be administered IV at 3 mg/kg. Subsequent dose levels of panobinostat and ipilimumab will be increased according to the schedule in Table 4.1.

Table 4.1 Dose Escalation regimen for Panobinostat and Ipilimumab

Dose Cohort	Panobinostat Dose	Ipilimumab Dose
1	5 mg po TIW	3 mg/kg
2	10 mg po TIW	3 mg/kg
3	15 mg po TIW	3 mg/kg
4	20 mg po TIW	3 mg/kg
-1	5 mg po TIW	1 mg/kg

Additional dose levels of panobinostat beyond the 20 mg PO TIW dose cohort may be added as appropriate, although it is expected that all subsequent doses will be no more than 33%

higher than the preceding dose (eg, from 20 mg PO TIW to 25 mg PO TIW). Start of induction cycle 1, Day 1 for the first 3 subjects should be separated by at least 1 day. During the DLT observation (within 84 days of initiation of study therapy), subjects, who for reasons other than study-drug related toxicity, either miss 1 or more of their scheduled doses of ipilimumab, or miss more than 10% of their scheduled Q12 hour doses of panobinostat, or do not complete the first induction cycle, will not be considered evaluable for safety for the purposes of dose escalation and will be replaced.

4.3.2 Administration of ipilimumab

Ipilimumab is to be administered as an IV infusion with a 1.2 μm in-line filter (see current version of Investigator's Brochure), using a volumetric pump, at the 3 mg/kg dose, and at an appropriate rate to complete the infusion in 90 minutes with a 10 cc normal saline flush at the end. Additional details on ipilimumab dose are outlined above in Section 4.1.1.1.
Refer to Section 4.3.8.1 regarding management of infusion reactions.

4.3.3 Dose Limiting Toxicity

For the purpose of guiding dose escalation decision making, hematologic and non-hematologic (hepatic versus non-hepatic) DLT will be defined separately and will be determined based on the incidence, severity, and duration of **study drug-related** AEs occurring within 84 days (12 weeks; through Day 42 of induction cycle 2) of initiation of study therapy. Using these features, the severity of AEs will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. For the purposes of subject management, DLTs will lead to dose modification regardless of the cycle in which a DLT occurs (see Section 4.3.8 for specific guidelines).

4.3.3.1 Definition of non hematologic dose-limiting toxicity

Non-hematologic dose-limiting toxicity (DLT) will be defined as follows:

A: Hepatic Non-Hematologic DLT

Any one of the following events will be considered a hepatic DLT (irrespective of whether it is considered to be an irAE):
Isolated Grade 4 AST/ALT
Isolated Grade 3 AST/ALT that fails to return to Grade 1 or less within 5 days
Isolated Total Bilirubin ≥ Grade 3 with AST or
ALT > 3 x ULN and concurrent total bilirubin > 2 x ULN

B: Non-Hepatic Non-Hematologic DLT

Any Grade 3 or greater non-hepatic non-hematologic toxicity will be considered as a dose-limiting toxicity with the following specific **exceptions**:

• Grade 3 electrolyte abnormalities that are not complicated by associated clinical adverse experiences, last less than 48 hours and either resolve spontaneously or respond to conventional medical intervention.
• Grade 3 nausea or vomiting that lasts less than 48 hours, and either resolves spontaneously or responds to conventional medical intervention.
• Isolated Grade 3 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis.
• Isolated Grade 3 fever that lasts ≤ 3 days and is not associated with hemodynamic compromise (ie hypotension, clinical or laboratory evidence of impaired end-organ

perfusion).

Criteria for Non-Hematologic DLT in Context of Immune-Related AEs and Infusion Reactions:
A constellation of immune-related adverse events (irAEs) have been observed in patients treated with ipilimumab monotherapy. Similarly, as has been seen with a broad range of therapeutic antibodies, infusion reactions have been observed among patients treated with ipilimumab. Based on broad clinical experience with ipilimumab, a unique set of criteria have been developed to define and manage dose-limiting toxicities in the context of irAEs and/or infusion reactions and are outlined below.

C: Immune-related Adverse Experiences (irAEs) and DLT
Definition of DLT in the context of irAEs will consider the incidence, severity, time of onset, duration and time to resolution for the specific irAE in the context of existing experience with ipilimumab. All Grade 3 or greater immune related AEs will be considered as potential DLTs. An independent DMC will be utilized to advise on aggregate safety data from this study and more specifically to review all Grade 3 or greater irAEs. Immune related AEs among patients treated with ipilimumab have clustered among skin, gastrointestinal, endocrine and liver-related events as follows:
Skin: alopecia, dry skin, hyperhidrosis, night sweats, pruritus, rash/desquamation, toxic epidermal necrolysis, urticaria, and vitiligo.
Gastrointestinal: abdominal discomfort or pain, anal ulcer, colitis (including ulcerative, haemorrhagic, ischaemic, and megacolon), constipation, cramping, diarrhea (including haemorrhagic), diverticulitis/diverticulum, duodenitis, dyspepsia, dysphagia, enteritis, esophagitis, gastritis (including erosive), gastrointestinal haemorrhage (including rectal), hematochezia, ileitis, ileus, intestinal obstruction, intestinal perforation (including small and large intestines), melena, nausea, pancreatitis, peritonitis, stomatitis (including aphthous), vomiting, vasculitis gastrointestinal.
Endocrine: adrenal insufficiency (including Addison's disease), glucose tolerance impaired, hyperthyroidism hypogonadism, hypophysitis/hypopituitarism (autoimmune), hypothyroidism, pituitary enlargement, thyroiditis (autoimmune).
Liver: hepatitis, jaundice

Dose-limiting immune-related AEs will be defined as the follows:
- Any Grade 2 or greater eye pain or reduction in visual acuity that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks of the initiation of topical therapy **or** any Grade 2 or greater eye pain or reduction in visual acuity that requires systemic treatment.
- Any other Grade 3 or greater irAE:

D: Infusion Reaction and DLT
Grade 3 or Grade 4 infusion reactions will also be considered as dose-limiting events.

4.3.3.2 Definition of hematologic DLT
Hematologic DLT will be defined as follows:
• Grade 4 neutropenia ≥ 7 days in duration
• Grade 4 thrombocytopenia, or any Grade 3 thrombocytopenia associated with clinically-significant bleeding

• Grade ≥ 3 febrile neutropenia
• Grade ≥ 3 hemolysis

4.3.4 Duration of Treatment

Subjects may remain on study therapy until progressive disease as determined by immune-related response criteria (irRC), withdrawal due to toxicity, withdrawal of consent, or at the discretion of the investigator.

4.3.5 Intra-subject Dose Escalation

Intrasubject dose escalation for panobinostat or ipilimumab is not permitted in order to allow better evaluation of extended safety and efficacy at individual levels.

4.3.6 Guidelines for Dose Modification

Patients who have not experienced a dose-limiting toxicity may continue on therapy if, in the opinion of the investigator, they are experiencing clinical benefit (i.e. stable disease or objective response as determined by irRC). For patients who experience a dose-limiting hematologic or non-hematologic toxicity, therapy should be held/deferred pending resolution of the toxicity.

Panobinostat/Ipilimumab Dose Modification Guidelines for Non-hematologic and Hematologic Events Other Than Infusion Reactions:

- Patients who experience hepatic non-hematologic DLT irrespective of irAE or any Grade 3 or greater irAE will be removed from study with no further dose reduction.
- For patients who experience a first episode of non-hepatic non-hematologic DLT or a first episode of hematologic DLT, therapy may be reinitiated at the next lowest panobinostat/ipilimumab dose level as specified below in Table 4.3 if the event has resolved to less than or equal to Grade 1 in severity at the time the next cycle is due.
- For patients who experience a second episode of either hematologic or non-hepatic non-hematologic DLT, a second dose reduction may be performed as specified below for the successive cycle if the second dose-limiting event is distinct in nature from the first event and the event has resolved to less than or equal to Grade 1 in severity at the time the next cycle is due.
- In the event of a DLT, successive cycles of therapy may be delayed up to 14 days pending resolution of the toxicity to grade 1 or less in severity. Patients on dose level #1 will not be dose reduced in the event of DLT. Patients on dose level #2 will be allowed a maximum of 1 dose reduction, with the second occurrence of DLT necessitating removal from study.
- Any patient who develops significant irreversible (i.e. more than 2 weeks after the last dose of study drug) organ dysfunction (i.e., Grade IV non-hepatic non- hematologic toxicity) or anaphylaxis considered to be related to study drug will also be removed from study with no further dose reduction.
- All cardiac events should be treated as per the local standard of care and referred to a specialist if clinically indicated. The readings of ECGs will use the Fridericia correction: QTcF. Any final decisions concerning dose modifications or permanently discontinuing the patient from study drug due to QTcF prolongation will be based on the

assessment of the principal investigator. If a patient cannot be dosed due to prolonged QTcF for more than 7 days since last dose, patient should be discontinued from study.

Table 4.2 Criteria for dosing delays, dose-reductions, and re-initiation of treatment due to study drug-related QTcF abnormalities

ECGs to be performed at specified time point	Abnormality Noted	Dose Modification Guideline - At any time during a cycle of therapy (including intended day of dosing)
Cycle 1 Day 1 dose modification criteria:		
Pre-dose on cycle 1, day 1 3 ECGs separated by at least 5 minutes, obtained prior to panobinostat dosing	Average QTcF > 450 msec	Check and correct the patient's serum potassium, magnesium, calcium and phosphorus immediately, as well as evaluate con-meds. Repeat 3 pre-dose ECGs. If the 3 pre-dose ECGs: Do not meet criteria again, discontinue patient from study. Do meet criteria for dosing; administer study drug treatment.

ECGs to be performed at specified time point	Abnormality Noted	Dose Modification Guideline - At any time during a cycle of therapy (including intended day of dosing)
Cycle 1 Day 5 dose modification criteria		
Pre-dose on cycle 1, day 5: 3 ECGs separated by at least 5 minutes, obtained prior to panobinostat dosing	Average QTcF: ≥ 480 msec to < 500 msec OR > 60 msec increase from baseline average	Check and correct the patient's serum potassium, magnesium, calcium and phosphorus immediately, as well as evaluate con-meds. Notify Sponsor and transmit to ERT immediately for prompt review. Repeat 3 pre-dose ECGs. If the 3 pre-dose ECGs: Do meet criteria for dosing; administer study drug treatment. Do not meet criteria again, delay dose until the next scheduled time point and repeat 3 pre-dose ECGs. If the repeat 3 pre-dose ECGs: Do not meet pre-dose ECG criteria again, discontinue patient from study. Do meet pre-dose ECG criteria for dosing and QT prolongation is determined to be related to study drug, resume study drug treatment with a dose reduction of one dose level. If however, it was determined that the QT prolongation was secondary to electrolyte abnormalities or con-meds, continue at the same dose level. Repeat ECGs - pre-dose (x3) on the next scheduled dosing day.
	Average QTcF ≥ 500 msec	Check and correct the patient's serum potassium, magnesium, calcium and phosphorus immediately, as well as evaluate con-meds. Notify Sponsor and transmit to ERT immediately for prompt review. Discontinue patient from study therapy If however, it was determined that the QT prolongation was secondary to electrolyte abnormalities or con-meds: omit dose. On the next scheduled dosing day continue at the same dose level. Repeat ECGs - pre-dose (x3), 3-hours post-dose (x3), on the next scheduled dosing day.

ECGs to be performed at specified time point	Abnormality Noted	Dose Modification Guideline - At any time during a cycle of therapy (including intended day of dosing)
Cycle 2 and beyond dose modification criteria:		
If required: Pre-dose on day 1 of each cycle 3 ECGs separated by at least 5 minutes, obtained prior to panobinostat dosing:	Average QTcF > 480 msec	Check and correct the patient's serum potassium, magnesium, calcium and phosphorus immediately, as well as evaluate con-meds. If abnormality noted: Repeat 3 pre-dose ECGs. If the 3 pre-dose ECGs: Do not meet criteria again, discontinue patient from the study. Do meet criteria for dosing; administer study drug treatment If, however, it was determined that the QT prolongation was secondary to electrolyte abnormalities or con-meds: Omit dose. On the next scheduled dosing day, continue at the same dose level. Repeat ECGs pre-dose (x3) on the next scheduled dosing day.
	Average QTcF ≥ 500 msec	Check and correct the patient's serum potassium, magnesium, calcium and phosphorus immediately. Discontinue patient from study therapy If however, it was determined that the QT prolongation was secondary to electrolyte abnormalities or con-meds: omit dose. On the next scheduled dosing day continue at the same dose level. Repeat ECGs - pre-dose (x3) on the next scheduled dosing day.

In the setting where dose modifications are required, doses of PANOBINOSTAT and ipilimumab will be reduced to doses for the cohort immediately preceding the current dose level. Dose modifications are provided in Table 4.3

Table 4.3 Dose Modification Guidelines for Panobinostat and Ipilimumab

Cohort	Ipilimumab Dose Panobinostat Dose	Dose Modification #1	Dose Modification #2
1	3 mg/kg	1 mg/kg	Off Study
	5 mg	5 mg	
2	3 mg/kg	3 mg/kg	Off Study
	10 mg	5 mg	
3	3 mg/kg	3 mg/kg	3 mg/kg
	15 mg	10 mg	5 mg
4	3 mg/kg	3 mg/kg	3 mg/kg
	20 mg	15 mg	10 mg
-1	1 mg/kg	Off Study	Off Study
	5 mg		

4.3.7 Supportive Care Guidelines

4.3.7.1 Guidelines For Infusion Reactions

Ipilimumab may induce infusion or hypersensitivity reactions. These reactions may manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo or hypertension, bronchospasm, or other symptoms. Infusion reactions should be graded according to Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0) guidelines. The Sponsor will be responsible for the appropriate notification of Study Investigators and the DMC of ≥ Grade 3 infusion reactions. Treatment recommendations and dose modification guidelines are provided below. Supportive care guidelines may be modified based on clinical judgment, local treatment standards and guidelines, and/or specific symptoms, as appropriate:
For Grade 1 symptoms: Mild reactions (localized cutaneous reactions including mild pruritus, flushing, rash),

- Decrease the rate of ipilimumab infusion until recovery from symptoms.
- Remain at bedside and monitor subject until resolution of symptoms.
- Diphenhydramine 50 mg, may be administered at the discretion of the treating physician.
- When symptoms resolve, restart the infusion at the original infusion rate
- Institute additional treatment as clinically indicated.

If a subject has a Grade 1 infusion reaction with ipilimumab, prophylactic preinfusion medications should be given prior to all subsequent ipilimumab infusions. The following prophylactic preinfusion medications are recommended in this setting to administered at least 30 minutes prior to ipilimumab administration;

- diphenhydramine 50 mg (or equivalent) and/or • acetaminophen 325 to 1000 mg

For Grade 2 symptoms: Moderate reactions [ie, any symptom not listed above (mild symptoms) or below (severe symptoms) such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic blood pressure > 80 mm Hg], require infusion interruption but respond promptly to symptomatic treatment [eg, antihistamines, non- steroidal anti inflammatory drugs, narcotics, corticosteroids, i.v. fluids]; prophylactic preinfusion medications indicated for ≤ 24 hours.

- Discontinue the study drug infusion.
- Begin an i.v. infusion of normal saline, and treat the subject with diphenhydramine 50 mg i.v. (or equivalent) and/or acetaminophen 325 to 1000 mg. • Remain at bedside and monitor subject until resolution of symptoms. • Corticosteroid therapy may be administered at the discretion of the treating physician.
- When symptoms resolve, restart the infusion at 50% of the original infusion rate; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate.
- Monitor subject closely. If symptoms recur, immediately discontinue the infusion; no further study drug will be administered at that visit. Administer diphenhydramine 50 mg i.v., and remain at bedside and monitor the subject until resolution of symptoms.

If a subject has a Grade 2 infusion reaction with ipilimumab, prophylactic preinfusion medications should be given prior to all subsequent ipilimumab infusions. The following prophylactic preinfusion medications are recommended in this setting to administered at least 30 minutes prior to ipilimumab administration;

- diphenhydramine 50 mg (or equivalent) and/or

- acetaminophen 325 to 1000 mg
- If considered necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: (Severe reaction [eg, bronchospasm, generalized urticaria, systolic blood pressure ≤ 80 mm Hg, or angioedema], Grade 3: prolonged [ie, requiring 6 or more hours to respond to symptomatic medication and/or discontinuation of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]. Grade 4: life-threatening; pressor or ventilatory support indicated).

- Immediately discontinue the study drug infusion. No further study drug will be given
- Begin an i.v. infusion of normal saline, and treat as follows: bronchodilators, epinephrine 0.2 to 1.0 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for i.v. administration, and/or diphenhydramine 50 mg i.v. with methylprednisolone 100 mg i.v. (or equivalent), as needed.
- Remain at bedside and monitor subject until recovery from symptoms. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur.
- The amount of study drug infused must be recorded on the case report form (CRF).
- In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids). In addition, Investigators should also follow their institutional guidelines for the treatment of anaphylaxis.

4.3.7.2 Guidelines for Management of Gastrointestinal AEs and

Endocrinopathies

Immune-related adverse events are well described with the use of ipilimumab. All subjects who receive treatment on this study should be closely monitored for any signs related to gastrointestinal or endocrine systems and aggressively managed at the first onset of clinical symptoms. A high index of suspicion for immune-mediated colitis should be maintained in subjects who present with diarrhea or other abdominal symptoms. Prompt initiation of appropriate therapy, including early administration of steroids should be instituted as consistent with the guidelines on management of diarrhea within the ipilimumab program (see Appendices 5-8). Specific algorithms for the management of immune-related AEs, diarrhea, hepatotoxicity, and endocrinopathies have been developed within the ipilimumab clinical program and are provided for reference in Appendices 5-8.

4.4 Blinding/Unblinding

This is an open label study. Blinding will not be utilized.

4.5 Destruction and Return of Study Drug

4.5.1 Destruction of Study Drug

If study drug panobinostat sourced by the investigator by Novartis are to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for the disposal, procedures for proper disposal have been established according to applicable regulations, guidelines and institutional procedures, and appropriate records documented.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.11 Screening Days -28 to -1

Procedure	Screening Visits	Notes
Eligibility Assessment	**X**	
Informed Consent	**X**	
Eligibility Criteria	**X**	
History	**X**	
Pathology review	**X**	
Physical examination	**X**	
Vital Signs	**X**	
Height and Weight	**X**	
Performance Status	**X**	
ECG	**X**	Single 12-lead ECG or triplicate if planned to be used as baseline (Induction Cycle 1 Day 1)
Chem panel, CBC	**X**	
Free T4, TSH, ACTH, Cortisol	**X**	
Liver and HIV serologies	**X**	HIV, HepBsAg, Hep C ab
PT/PTT	**X**	
Pregnancy test	**X**	Serum
Urinalysis	**X**	
Ophthalmologic exam	**X**	With slit lamp as a baseline
Tumor assessment	**X**	CT C-A-P with contrast, and unless contraindicated, MRI brain with gadolinium
Tumor Biopsy	**X**	Voluntary

Table 5.12 During Treatment, Day 1 onward

Study Cycle		Induction Cycle					Maintenance Cycle	End of Treatment	Follow-up	Notes
Cycle #	1				2		Each Cycle			
Day of Cycle[1]	1	5	22	35	1	22				
Safety Assessments										
Physical exam	X[2]		X		X	X	X	X	X	
Ophthalmology Exam	X									Baseline only
Vital Signs	X		X		X	X	X	X	X	
Weight	X		X		X	X	X	X	X	
PS	X[2]		X		X	X	X	X	X	
ECG	X[2, 3]	X[3]			X		X	X		Triplicate 12-lead for Induction Cycle 1 Day 1 & Day 5; single 12-lead ECG otherwise
Chem Panel, CBC	X[2]		X		X	X	X	X	X	
PT/PTT	X[2]									
T4, TSH	X[2]		X		X	X	X			
Serum Preg	X[2]						X			
Urinalysis	X[2]				X		X			
SAE Monitoring	X		X		X	X	X	X	X	
Ipilimumab	X		X		X	X				
Panobinostat	X		X		X	X	X[5]			
Disease Assessment					X		X	X	X	
PD Blood	X		X		X	X	X	X		
Tumor bx				X[4]						

[1] All study visits may be scheduled +/- 3 days from planned visit date.
[2] These tests will not be repeated on Cycle 1 Day 1 of the initial treatment period if completed for screening less than 72 hours (3 days) before the first dose of the study drugs.
[3] Triplicate ECGs at least 5 minutes apart will be done pre-dose on C1 D1 & C1 D5.
[4] Biopsy to be done between Days 35 and 42.
[5] Panobinostat will continue to be administered thrice weekly during the maintenance cycles.
6. Patients will continue to be followed for PFS and OS.

5.2 Study Materials

The Moffitt Cancer Center provide all of the required equipment for safe drug administration including all therapies as well as equipment for proper storage of study documentation, storage of clinical supplies, and processing of laboratory samples. The site will provide medications required for standard treatments. A current and fully- stocked advanced cardiac life support (ACLS) cart including resuscitation equipment and other agents to treat anaphylaxis (see Section 4.3.4) will be immediately available on the premises. The site will provide all materials required for accurate source documentation of study activities.

Case report forms (electronic or hard copy) will be provided by the Moffitt Clinical Trials Office. Novartis will provide panobinostat and ipilimumab will be from commercial stock.

5.3 Safety Assessments

All subjects who receive at least one dose of panobinostat and or Ipilimumab will be evaluated for safety parameters. Additionally, any occurrence of an SAE from time of consent until 90 days post discontinuation of study drug dosing will be documented. Safety will be evaluated for all treated subjects using the NCI CTCAE version 4.0. Safety assessments will be based on medical review of AE reports and the results of vital sign measurements, physical examinations and clinical laboratory tests. The incidence of AEs will be tabulated and reviewed for potential significance and clinical importance. The schedule or required visits, tests, procedures and assessments are described in the Procedural Outline Tables. In limited instances, scheduled evaluations can occur outside of this time frame but only within the windows noted. Please see the Procedural Outline Tables for a comprehensive list of assessments/procedures (Section 5.1). If the screening evaluation (physical exam, physical measurements, ECOG status and laboratory tests) is conducted within the 72 hour window of the first dose of panobinostat, then a single evaluation for these assessments may count for screening and pre-dose evaluation. If a subject has a delay in study drug administration for any reason, then assessments, laboratory tests and scans will be correspondingly delayed.

A screening 12-lead ECG will be performed to assess study eligibility. Additional 12-lead ECGs will be performed at a minimum at scheduled time points as indicated in Table 5.12. For all patients, a minimum of 3 sequential 12-lead ECGs, separated by at least 5 minutes, must be performed on cycle 1 day 1 prior to the first administration of oral panobinostat or within 72 hours prior to that day in order to get an accurate baseline QTcF calculation. Additionally, triplicate ECGs will be performed on cycle 1 day 5. The recommended dose modifications due to QTc interval prolongation are outlined in section 4.3.6.

5.3.1 Laboratory Test Assessments

A local laboratory will perform the analysis and will provide reference ranges for these tests. Results of clinical laboratory tests should be available for review prior to dosing on Day 1 of each treatment cycle. For other visit days, laboratory tests results should be reviewed within 24 hours of the visit. With the exception of laboratory assessments prior to the first dose of panobinostat/Ipilimumab, all laboratory tests can be performed within 24 hours prior to the scheduled visits. Laboratory assessments prior to the first dose of panobinostat/Ipilimumab may be performed up to 72 hours prior to the scheduled visits.

The following clinical laboratory tests will be performed:

Hematology

Hemoglobin Hematocrit Total leukocyte count, including differential Platelet count

Serum Chemistry

Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Direct bilirubin, if total bilirubin > ULN Alkaline phosphatase

Lactate dehydrogenase (LDH) Creatinine Blood Urea Nitrogen (BUN) or Urea Amylase Lipase

Serology
Uric Acid Glucose Total Protein Albumin Sodium Potassium Chloride Calcium Phosphorus Magnesium Bicarbonate; HepB, HepC, HIV (at screening only)
Other Assays
T4/TSH
Urinalysis
Protein Glucose Blood Leukocyte esterase Microscopic examination of the sediment if blood, protein or leukocyte esterase are positive on the dipstick
Coagulation Profile
PT/INR aPTT
Other Analyses
Pregnancy test (WOCBP only) FSH (if needed to document post-menopausal status as defined in Section 3.3.3)

At the investigator's discretion, laboratory tests may be repeated if clinically significant. If the units of a test result differ from those printed on the CRF, the recorded laboratory values must specify the correct units. Any abnormal laboratory test result considered clinically significant by the investigator must be recorded on the appropriate AE page of the CRF (see Section 6.2 Laboratory Test Abnormalities).

5.4 Efficacy Assessments

In this study, immune-related Response Criteria (irRC; see Appendix 4) will be used to assess subject response to study treatment and guide clinical care. However, response- based assessments in this study will be captured using both modified irRC and RECIST 1.1. The investigator will determine the irRC response at each tumor assessment. The RECIST 1.1 response for the patient will be calculated from the tumor assessment data by the Sponsor and will be used for reporting purposes. The RECIST 1.1 criteria will be used to determine subjects' best overall response (BOR), and for statistical analysis of efficacy in this study. Assessments of tumor status will be made during screening and then at 6 and 12 weeks and then every 12 weeks thereafter. The irRC represent modifications of the modified WHO criteria reflecting the clinical experience with ipilimumab in the completed and/or ongoing clinical studies in which objective and durable responses (as per mWHO) were observed in subjects following progression and without intervening alternative anti-cancer therapy. As such, the irRC are designed to capture clinical activity of ipilimumab immunotherapy that may not be adequately addressed by the RECIST 1.1 criteria and will only be used for patient management decisions, not formal efficacy reporting.

[redacted]

6 ADVERSE EVENTS

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. 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.)

6.1 Serious Adverse Events

A ***serious AE (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 which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- 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.)

Suspected transmission of an infectious agent (eg, any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE. Although pregnancy, overdose and cancer are not always serious by regulatory definition, these events must be handled as SAEs for data transmission purposes (See Section 6.1.1 for reporting pregnancies).

NOTE: The following hospitalizations are not considered SAEs:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered "important medical event" or event life threatening)
- elective surgery, planned prior to 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).

6.1.1 Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. SAEs (except those events considered secondary or related to disease progression) should be followed to resolution or stabilization. Follow-up is also required for SAEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate. The investigator should collect any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure. An SAE report should be completed for any event where doubt exists regarding its status of seriousness. If the investigator believes that an SAE is not related to study drug, 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 Report Form.

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 institutions initial receipt of the information. SAEs may be reportable to the FDA for both FDA-approved (post-market) drugs as well as investigational agents.

For an event to be reportable to the FDA, it must meet both of the following requirements as determined by the principal investigator of the study:

1. The event is possibly, probably or definitely related to the agent
2. The event is unexpected (i.e., not listed in the protocol, investigational brochure, or informed consent)

SAEs may be reportable to the FDA for both FDA-approved (post-market) drugs as well as investigational agents.

Reporting events for an APPROVED, POST-MARKET AGENT:

The current MedWatch mandatory reporting form FDA 3500A can be found on the FDA website:

http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm

Use: Form FDA 3500A - Mandatory Reporting

Complete the ***MedWatch*** report and mail it to the appropriate address below:

For Drugs:
Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

For Biologics, including Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps):
Center for Biologics Evaluation and Research
OBE Division of Epidemiology, (HFM-220)
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

To report an event for an INVESTIGATIONAL AGENT under investigational new drug applications:

Send a narrative of the event with circumstances, IND number, and why it is related and unexpected to the H. Lee Moffitt Cancer Center Regulatory Affairs IND Office.. A MedWatch report for the event would suffice. These events should not be reported or sent directly to the FDA by the study coordinator. The Regulatory Affairs IND Office at Moffitt Cancer Center will submit the reportable event as an IND safety report to the FDA on behalf of the principal investigator.

If the principal investigator determines that the event could be possibly related and unexpected to *both the post-market agent and the investigational agent*, then the following should be done:

- Submit the MedWatch report to the appropriate post-market address at the FDA as written above.
- Send the MedWatch report to regulatory affairs. The office will submit and IND safety report on the behalf of the principal investigator.

Reporting SAEs to Novartis
In addition to the reporting guidelines above, all SAEs, regardless of causality, should be reported to Novartis within 24 hours of becoming aware of the event. SAEs may be submitted in any format, using the fax cover sheets in Appendix 8.

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.)
If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to FDA using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug and continue through the day 90 follow-up visit with no new nonserious adverse events being reported past the end of treatment visit unless believed to be related to study drug. Post the EOT visit any ongoing AE's should be followed to resolution or stabilization, through the

day 90 follow-up, or reported as SAE's if they become serious (see Sections 6.1.1). Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects. Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate. Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.3 Laboratory Test Abnormalities

The following laboratory abnormalities should be captured as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical, rather than the laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

6.4 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject or a female partner of a male study participant 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 for the female study participant in an appropriate manner (eg, dose tapering if necessary for subject safety). Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported. Any pregnancy that occurs in a female partner of a male study participant should be reported to the IRB.

6.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as SAEs (see Section 6.1.1 for reporting details).

6.6 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 as a nonserious or serious AE, as appropriate, and reported accordingly.

7 DATA MONITORING COMMITTEE

To provide independent oversight for safety, study conduct and risk-benefit-ratio, an independent DMC made up of Moffitt faculty from the SPORE IAC and a patient advocate will provide oversight to this combination study of panobinostat with ipilimumab in subjects with melanoma. This committee will strictly serve in an advisory capacity to the study team. The committee will periodically review aggregate data from the study, specifically review all cases of Grade 3 or greater irAEs and will advise the study team regarding subject management, continuation, modification or discontinuation of dose regimens as appropriate. A charter detailing the activities of this DMC is available.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

Dose Escalation: This is a Phase I dose escalation trial and the sample size at each dose depends on the observed toxicity; however a total of 36 subjects for the dose-escalation study allows sufficient number of subjects if needed, e.g. more than 6 subjects if dose-limiting toxicities are observed among 2 of 6 subjects, to better estimate the toxicity rates per dose, and more accurately determine the MTD. Cohorts of 3 subjects with expansions to 6, or possibly even 9 or 12 subjects will be treated at each suggested dose level until MTD is determined.

In this protocol, we will be using a new phase I trial approach (Table 8.1), modified from a design from Ji et al[43]. This approach provides a broader phase I experience than the traditional 3+3 design, thus allowing for a more robust choice of an MTD. While setting the target toxicity rate at 18%, this design allows further examination of a dose when 2 DLTs occur among 6 patients, while still keeping the observed toxicity at the MTD well managed (it is below 26% for sample sizes $\geq$ 9). The trials will enroll up to 36 patients for determination of the MTD, but will be successfully concluded earlier if 12 patients are accrued at the dose determined to be the MTD, with 3 DLTs. If, at any time, one de-escalates to a dose which has already accrued 12 patients, the study will be terminated and that dose declared to be the MTD. The MTD is obtained at 33 patients if 9 or 12 patients have been accrued at the current dose and the dose is acceptable (E, S or C). Otherwise, if the current dose has $\leq$1 of 3, or $\leq$2 of 6 DLTs, then three more patients will be accrued at that dose – if at most 1 of 6, or 2 of 9 have DLTs, that dose is the MTD.

Table 8.1 Decision Rules on dose escalation based on number of DLTs**

N*	Observed DLTs per cohort and treatment decisions												
		0		1		2		3		4		5		6
3		E		S		DU		DU	-	-	-	-	-	-
6		E		E		S		DU		DU		DU		DU
9		E		E		S		D		DU		DU		DU
12		E		E		E		C		DU		DU		DU

N* =number of subjects treated at a given dose level
S: stay at the same dose and enroll a cohort of 3 more subjects at that dose
E: escalate to the next higher dose by enrolling 3 more subjects

D: de-escalate to the lower dose, and enroll 3 more subjects at the lower dose, or
DU: declare the current dose as unacceptable and unsafe, de-escalate to the lower dose, and enroll 3 more subjects at the lower dose
C: Study completed and dose is declared to be the MTD
**for MTD target toxicity pT=18%, and allowing any dose with pT in (17%, 19%) to be selected
The modifications involve escalating the dose whenever the observed toxicity rate is below 17% and using the N-1st patient to define the change when the toxicity rate exceeds 19% and $N \geq 9$ to account for the fact that the design is being used in cohorts of 3 rather than continuously as designed by Ji et al[43].

8.2 Endpoint Definitions

8.2.1 Safety Endpoints

All subjects who receive study any drug therapy will be evaluated for safety. 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. Triplicate 12-lead electrocardiograms (ECGs) will be collected prior to dosing on Day 1 of induction cycle 1. Single 12-lead ECGs will be collected at screening, prior to dosing on Day 1 of each treatment cycle and at the end of treatmentvisit.
Adverse events will be categorized using the most current version of MedDRA and adverse events and laboratory tests will be graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Immune-related adverse experiences (irAEs) among treated subjects will be specifically assessed as well.

8.2.2 Efficacy Endpoints

8.2.2.1 Efficacy Endpoints based on RECIST 1.1

The best overall response (BOR), computed for all treated subjects, is defined as the best response designation over the study as a whole, recorded between the dates of first dose until the last tumor assessment prior to subsequent therapy.
Objective Response Rate (ORR) is defined as the total number of subjects whose best response outcome is a complete response (CR) or partial response (PR) divided by the total number of evaluable subjects.
Disease Control Rate (DCR) is defined as the total number of subjects whose best response outcome is a complete response (CR) or partial response (PR), or stable disease divided by the total number of evaluable subjects.
Prolonged Disease Control Rate (PDCR) is defined as the total number of subjects whose best response outcome is a complete response (CR) or partial response (PR), or stable disease lasting at least 12 weeks, divided by the total number of evaluable subjects.
Progression Free Survival (PFS): is defined for each subject as the time from first dosing to the first observation of disease progression or death due to any cause. If a subject has not progressed or died at the time of analysis, PFS will be censored on the date of the last disease assessment. Subjects who do not have any tumor assessment on treatment will be censored on the day of the first dose.
Duration of Overall Response: will be computed for all subjects whose best response is either a PR or CR and is calculated from the time the measurement criteria are met for PR or CR, whichever is recorded first, until the date of documented progressive disease or death.

Duration of Disease Control: will be computed for the subjects who had BOR outcome of CR, PR, or Stable Disease and is calculated from the beginning of treatment until the time of documented disease progression.

8.2.2.2 Efficacy Endpoints based on Immune Related Criteria (irCR)

Immune Related Best Overall Response (irBOR) is the best irRC designation over the study as a whole, recorded between the date of first dose until the last tumor assessment prior to subsequent therapy (except for local palliative radiotherapy for painful bone lesions) for the individual subject in the study. 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.
Immune-related Response Rate (irRR) is defined as the proportion of response evaluable subjects whose irBOR outcome is irPR, irCR.
Immune-related Disease Control Rate (irDCR) is defined as the proportion of the response evaluable subjects whose irBOR outcome is irPR, irCR, or irSD.
Immune-related Prolonged Disease Control Rate (irPDCR) is defined as the proportion of the response evaluable subjects whose irBOR outcome is irPR, irCR, or irSD, with stable disease lasting at least 12 weeks.
Immune-related Progression-Free Survival (irPFS) is defined as the time between the first dosing date and the date of irPD or death, whichever occurs first. For subjects with no recorded post-baseline tumor assessment, irPFS will be censored at the day of first dose. A subject who dies without reported irPD will be considered to have progressed on the date of death. For those who remain alive and have no irPD, irPFS will be censored on the date of last evaluable tumor assessment. Subjects who do not have any tumor assessment on treatment will be censored on the day of the first dose.
Duration of Immune Related Overall Response: will be computed for all subjects whose irBOR outcome is either an irPR or irCR and is calculated from the time the measurement criteria are met for irPR or irCR, whichever is recorded first, until the date of documented progressive disease or death by irRC.
Duration of Immune Related Disease Control: will be computed for the subjects who had irBOR outcome of irCR, irPR, or ir Stable Disease and is calculated from the beginning of treatment until the time of documented disease progression by irRC.

[redacted]

8.3 Analyses

8.3.1 Demographics and Baseline Characteristics

Frequency distributions of gender and race will be tabulated by dose. Summary statistics for age, body weight, height, and Body Mass Index (BMI) will be tabulated by dose.

8.3.2 Efficacy Analyses

Listings of tumor measurements will be provided by subject and study day in each arm. Individual subject's best overall response (BOR) and progression free survival (PFS) will be listed based on RECIST 1.1 (dose escalation and cohort expansion). To describe the anti-tumor activity of panobinostat administered in combination with ipilimumab, Objective Response Rate (ORR) as well as prolonged disease control rate by RECIST 1.1 (PDCR) will be similarly summarized. Objective Response (OR) is defined as BOR outcome of CR or PR by RECIST 1.1. Disease Control (DC) defined as BOR outcome of CR, PR, or Stable Disease by RECIST 1.1. Prolonged disease control is defined as disease control with stable disease of at least 12months. Duration of response and duration of disease control will also be calculated for the subjects with such outcome, based on both efficacy criteria. Median PFS, Duration of Response, and Duration of Disease Control will be estimated by Kaplan-Meier method and with 95% confidence intervals, at the MTD based on both response criteria. Kaplan Meier plots will be provided for all time-to-event variables at the MTD, based on both response criteria. We will also fit the survival function using a parametric survival approach, as this approach provides a more accurate estimate of the median PFS Additional assessments, e.g. sensitivity analyses may be performed to characterize clinical activity. The relationship between panobinostat exposure/dose and clinical efficacy (e.g. tumor response based on RECIST 1.1 criteria) may be explored graphically and appropriate model may be fit.

8.3.3 Safety Analyses

All recorded adverse events will be listed and tabulated by system organ class, preferred term, and dose and coded according to the most current version of MedDRA. The incidence of adverse events will be tabulated and reviewed for potential significance and clinical importance. Vital signs and clinical laboratory test results will be listed and summarized by and dose. Any significant physical examination findings and results of clinical laboratory tests will be listed. ECG listings will be evaluated by the investigator and abnormalities, if present, will be listed. A separate listing and summary of all immune-related adverse events (irAE) and inflammatory events regardless of causality (IERC) will be provided. In addition, the irAE rate will be estimated and a 90% confidence interval will be constructed for the irAE and the grade 3-4 GI irAE rate in each arm, based on the Clopper-Pearson method. The relationship between panobinostat exposure/dose and adverse event may be explored graphically and appropriate model may be fit.

8.3.4 Biomarker Analyses

[redacted]

Pharmacodynamic analyses will examine the patterns of change in ALC over time, and how these patterns might differ between treatment arms. Predictive analyses will examine potential relationships between ALC and measures of response such as PFS or irPFS. The mean rate of change in ALC over time and corresponding two-sided 95% CIs will be estimated using an extended linear model, fit by restricted maximum likelihood (REML). The model will have fixed effects of treatment and time since first dose. Predictive analyses will assess the relationship between PFS / irPFS and rate of change in ALC over time (ALC slope). Summary statistics for peripheral blood biomarkers of immunoregulatory activity such as, but not limited to T-cell subpopulation counts, serum cytokines, and their corresponding changes (or percent changes) from baseline will be tabulated by planned study day and dose in each arm, to assess pharmacodynamic effects. In addition, the time course of biomarker measures will be investigated graphically; if there is indication of meaningful pattern across time, further analysis (eg, by linear mixed models) may be performed to characterize the relationship. Possible associations between changes in biomarker measures of interest and panobinostat exposure will be explored graphically. Summary statistics for measures and changes from baseline of tumor-based markers including T-cell (CD4, CD8, CD45, FoxP3) and apoptosis markers (IDO and granzyme B) will be tabulated by study visit for each arm. Results from mRNA expression profiles pre- and on-treatment, in peripheral blood and fresh tumor biopsies and from T cell phenotype analysis on baseline samples will be tabulated, and possible associations with clinical outcome (e.g. tumor response) will be explored based on data availability. Associations between biomarkers and efficacy measures will be analyzed in all response-evaluable subjects. Methods such as, but not limited to, logistic regression will be used to explore possible associations between biomarker measures from peripheral blood or tumor markers and clinical outcome, e.g. tumor response, based on both RECIST 1.1 and irRC criteria.

9 STUDY MANAGEMENT

9.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this protocol. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment. Any significant deviation must be documented in the CRF. If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to: IRB/IEC for review and approval/favorable opinion. Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) will be sent to Novartis. If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment. If the revision is an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.2 Monitoring

This study will be monitored internally by the Moffitt Cancer Center Monitoring Core.

Representatives of Novartis will be allowed to visit the study site periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. The investigator must notify Novartis promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to Novartis.

9.3 Records

9.3.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the sponsor, whichever is longer. The investigator must contact Novartis prior to destroying any records associated with the study. If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB).

9.3.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (panobinostat supplied by Novartis) is maintained at the study site. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label ID number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage • non-study disposition (eg, lost, wasted) • amount destroyed at study site, if applicable • amount returned to the sponsor
- retain samples for bioavailability/bioequivalence, if applicable • dates and initials of person responsible for Investigational Product (IP) dispensing/accountability, as per the Delegation of Authority Form.

The sponsor will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.3.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained. The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s). The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs. The completed CRF, including any paper SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by a qualified physician who is an investigator or sub-investigator.

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APPENDIX 1 – ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS

Performance Status Criteria	
ECOG (Zubrod)	
Score	**Description**
0	Fully active; able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry on normal activity; minor symptoms of disease
2	Ambulatory and capable of all self care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of only limited self care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self care; totally confined to bed or chair.

APPENDIX 2 – CYP3A4 INHIBITORS, INDUCERS, AND SUBSTRATES

CYP3A4 INHIBITORS, INDUCERS, AND SUBSTRATES

The following list describes medications and foods which are common inhibitors, inducers, or substrates of CYP3A4. These medications should be used with caution during this study. This list should not be considered all inclusive. Consult individual drug labels for specific information on a compound's propensity to inhibit CYP3A4.

STRONG CYP3A4 INHIBITORS
atazanavir indinavir nelfinavir ritonavir saquinavir clarithromycin itraconazole ketoconazole

STRONG CYP3A4 INDUCERS
rifampin carbamazepine phenytoin phenobarbital St. John's wort
mibefradil nefazodone telithromycin cyclosporin troleandomycin verapamil grape fruit seville orange

CYP3A4 SUBSTRATES WITH NARROW THERAPEUTIC INDEX
alfentanil astemizole cisapride cyclosporine diergotamine ergotamine
Revised Protocol No.: 01 Date: 30-Sep-2010
fentanyl pimozide quinidine sirolimus tacrolimus terfenadine

OTHER CYP3A4 SUBSTRATES, INHIBITORS AND INDUCERS CYP3A4 SUBTRATES
Macrolide antibiotics: clarithromycin erythromycin NOT azithromycin telithromycin
Anti-arrhythmics: quinidine Benzodiazepines: alprazolam diazepam midazolam triazolam
Immune Modulators: cyclosporine tacrolimus (FK506)
HIV Protease Inhibitors: indinavir ritonavir saquinavir
Prokinetic: cisapride
Antihistamines: astemizole chlorpheniramine
Calcium Channel Blockers: amlodipine diltiazem felodipine
nifedipine nisoldipine nitrendipine verapamil
HMG CoA Reductase Inhibitors: atorvastatin cerivastatin lovastatin
NOT pravastatin simvastatin
Others: aripiprazole buspirone gleevec haloperidol (in part) methadone pimozide quinine NOT rosuvastatin sildenafil tamoxifen trazodone vincristine

CYP3A4 INHIBITORS
amiodarone NOT azithromycin cimetidine

CYP3A4 INDUCERS
HIV Antivirals: efavirenz nevirapine
diltiazem erythromycin fluvoxamine
Others: barbiturates glucocorticoids modafinil troglitazone rifabutin

APPENDIX 3 – RECIST 1.1 CRITERIA

RECIST 1.1 CRITERIA

- Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

− *Measurable disease:* the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

− *Measurable lesions:* lesions that can be accurately measured in 2 perpendicular diameters with at least one diameter ≥ 20 mm using conventional techniques or ≥ 10 mm with spiral CT scan *using a 5 mm contiguous reconstruction algorithm.*

− *Non-measurable lesions:* all other lesions, including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonitis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques.

- All measurements should be taken and recorded in metric notation, using a ruler or calipers. *All lesion measurements must be recorded in millimetres (or decimal fractions of centimetres).*
- All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than approximately 30 days before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of measurement

- CT and MRI are the best currently available and reproducible methods to measure index lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline documentation of "index" and "non-index" lesions

- All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as **index lesions** and recorded

and measured at baseline.

- Index lesions should be selected on the basis of their size (lesions with the longest diameter and perpendicular diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the longest diameters for *all index lesions* will be calculated and reported as the baseline sum. The baseline sum will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as **non-index lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend of the achievement of both measurements and confirmation criteria.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.
- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol.

APPENDIX 4 – IMMUNE RELATED RESPONSE CRITERIA

Immune Related Response Criteria

4.1 Tumor Assessments

The immune-related Response Criteria (irRC) is a further refinement of the mWHO criteria to better capture tumor responses in subjects on immunotherapy. The irRC was developed/implemented to address the difference in the natural history of the clinical responses observed in subjects treated with immunotherapy agents which differs from those seen in subjects on other classes of anti-cancer agents.

Differences of response patterns between cytotoxic and immune therapies are now recognized by the scientific community[1] as well as by Regulatory Authorities[2]. These differences have been characterized by Wolchok[3] et al after a post hoc analysis of the radiological responses that were observed during the Phase 2 studies performed in melanoma:
• The appearance of measurable antitumor activity may take longer for immune therapies than for cytotoxic therapies;
• Responses to immune therapies may occur after conventional PD; •
Discontinuation of immune therapy may not be appropriate in some cases, unless PD is confirmed (as is usually done for response);
• Allowance for "clinically insignificant" PD (eg, small new lesions in the presence of other responsive lesions) is recommended;
• Durable SD may represent antitumor activity.
These observations lead to the development or immune-related Response Criteria extensively described by Wolchok et al[3], used to define efficacy endpoints in more recent ipilimumab studies.

4.2 Radiological Assessment of Tumor Lesions

4.2.1 CT/MRI

CT/MRI imaging of the chest and abdomen is required at Screening and at each tumor assessment (TA), regardless of the location of known metastases. In addition, CT/MRI scans must be obtained of anatomic regions not covered by the chest and abdomen scans in subjects where there is clinical suspicion of deep soft tissue metastases (eg, lesions in the thigh). Such additional CT/MRIs will be required at Screening only when deep soft tissue disease is known/suspected and must be consistently repeated at all TAs if a deep soft tissue lesion is identified during Screening. The same imaging modality must be used at all TAs.
Brain scans are required at Screening to rule out CNS metastases. Brain scans to be repeated as clinically indicated. Contrast enhanced CTs are preferred, MRIs are a second choice.
Similar methods of TA and similar techniques must be used to characterize each identified and reported lesion at Screening and all subsequent tumor assessments. Imaging-based evaluation is preferred to clinical examination. Helical (spiral) CT scans of the chest and abdomen are preferred. If not available, conventional (non helical, non- spiral CT) should be used; however, a measurable lesion must not have the longest diameter smaller than 20 mm.
IV contrast should be used for all CT scans; if IV contrast is contraindicated, oral contrast maybe used, or MRI should be used at the Screening exam and at all TA time points.
Subjects who develop contrast allergy after study enrollment must be followed by MRI for subsequent tumor measurements.

A reference measurement ruler must be printed on every image for scale determination. Sections should be contiguous, similarly sized and consistent from visit-to-visit. Section thickness must be based on institutional standards (e.g, from 5 to 8 mm, 10 mm cuts are not recommended). Chest x-rays and ultrasound are not acceptable methods to measure disease.

4.2.2 Bone Scans

Assessment of irPD is never based only on a new lesion(s) found on bone scans. However, if bone lesions are identified at any time during the study, additional imaging studies of the lesion(s) must be performed to confirm the malignant nature of the new findings on the bone scan. If an abnormal bone scan was observed at any time point throughout the study, a new bone scan must be performed prior to the confirmation of a complete response (eg, the remaining metastastic lesions must have resolved). In case of new lesions such as pleural effusion, cytology must be performed to identify and confirm malignancy. Skin and soft tissue lesions will be captured as non-measurable lesions through physical examination only.

4.3 Definition of Measurable / Non-Measurable Lesions

- Measurable lesions are lesions that can be accurately measured in 2 perpendicular diameters, with at least one diameter ≥ 20 mm and the other dimension ≥ 10 mm (10 mm x 10 mm for spiral CT with cuts of 5 mm). The area will be defined as the product of the largest diameter with its perpendicular.
- Non-measurable (evaluable) lesions are all other lesions, including unidimensional 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.

4.4 Definition of Index / Non-Index Lesions

Measurable lesions, up to a maximum of **five lesions per organ and ten lesions in total,** must be identified as *index* lesions to be measured and recorded on the CRF at Screening. The *index* lesions should be representative of all involved organs. In addition, *index* lesions must be selected based on their size (eg, lesions with the longest diameters), their suitability for accurate repeat assessment by imaging techniques, and how representative they are of the subject's tumor burden. At Screening, a Sum of the Products of Diameters (SPD) for all *index* lesions will be calculated and considered the baseline SPD. The baseline sum will be used as the reference point to determine the objective tumor response of the *index* lesions at 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 CRF and will be evaluated at the same assessment time points as the *index* lesions. In subsequent assessments, *non-index* lesions will be recorded as complete response, stable or progression.

All measurable and non-measurable lesions should be assessed at Screening and at the defined TA time points. Extra assessments may be performed, as clinically indicated, if there is a suspicion of progression. The Investigator will base response to treatment using the irRC.

4.5 Definition of New Lesions

New lesions (both measurable and non-measurable) will be recorded on the appropriate CRF

for any tumor assessment. The appearance of up to 10 new lesions should be recorded. Once a new lesion has been identified ir should be reassessed at each subsequent TA time point using the same imaging modality. If meaurable, the dimensions of the new lesions should be recorded on the CRF, as they will be used to calculate the irSPD.

4.6 Tumor Response Using Immune-Related Response Criteria (irRC)

4.6.1 Confirmation Scans

Any subject who develops an objective tumor response (irCR or irPR) is recommended to undergo confirmatory scans no less than 4 weeks since the prior scan in order to verify the reliability of the radiologic finding.
It is also recommended that any subject that develops ir-progressive disease (irPD) also undergo confirmatory scans no less than 4 weeks since the prior scan to verify the reliability of the radiologic finding before discontinuation of all study treatment.

4.6.2 Calculation of Sum of Product of Diameters (SPD) for irRC (irSPD)

SPD is an estimation of tumor burden. The two greatest perpendicular diameters are used to estimate the size of each tumor lesion. The SPD is calculated as the sum of the product of the diameters for index tumor lesions. Several variations of the SPD are identified for the purpose of classification of tumor responses.
SPD at Baseline: The sum of the product of the diameters for all index lesions identified at baseline prior to treatment on Day 1. Immune-related SPD (irSPD) at baseline is the same as SPD.
SPD at TA: For every on-study TA collected, per protocol Section 5.1 or as clinically indicated, the SPD at TA will be calculated using tumor imaging scans. An index lesion and all new measurable lesions that have emerged after baseline will contribute to SPD at TA. Therefore, the SPD at TA using the irRC for progressive disease incorporates the contribution of new measurable lesions. Each net percentage change in tumor burden per assessment using irRC accounts for the size and growth kinetics of both old and new lesions as they appear.
SPD at Nadir: For tumors that are assessed more than one time after baseline, the lowest value of the SPD (SPD Baseline or SPD at TA) is used to classify progression at subsequent TAs for each subject.

4.6.3 Impact of New Lesions on irRC

New lesions alone 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 for tumor response. Therefore, new non-measurable lesions will not discontinue any subject from the study. Definition of Best Overall Response using irRC (irBOR) will be based on the following 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 irCR.
• 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 TA, 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 the Product of the Diameters (irSPD). A decrease, relative to baseline of

the irSPD of 50% or greater is considered an irPR. This must be confirmed no less than 4 weeks from the first 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 at the following TA. Any of the following will constitute progressive disease:
  - At least a 25% increase in the SPD of all index lesions and new measurable lesions (irSPD) over the nadir SPD calculated for the index lesions.

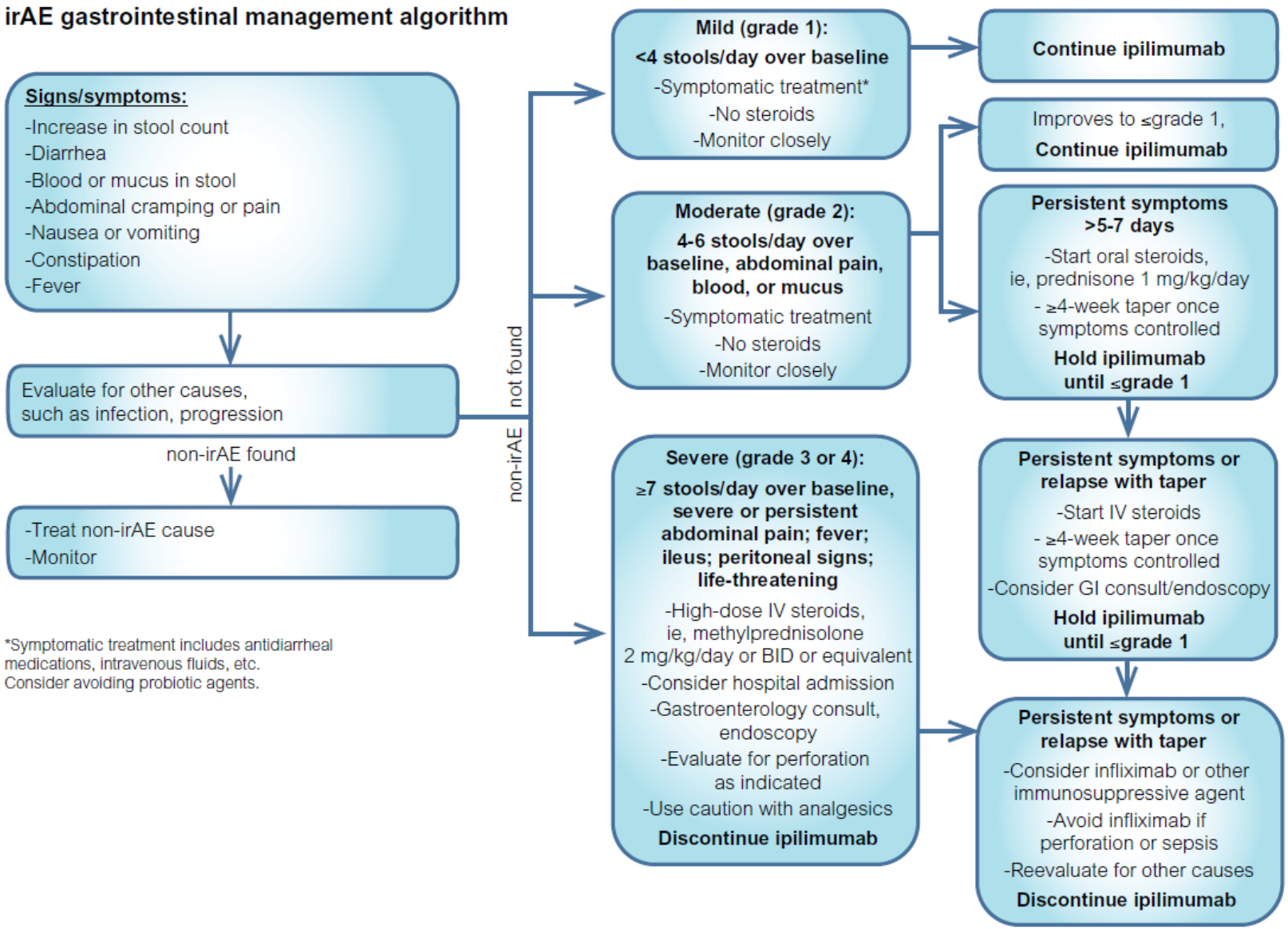
References:

1 Guidance for Industry. Clinical Consideration for Therapeutic Vaccines. Draft guidance. FDA. http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm182443.htm. Accessed 12-03-09.

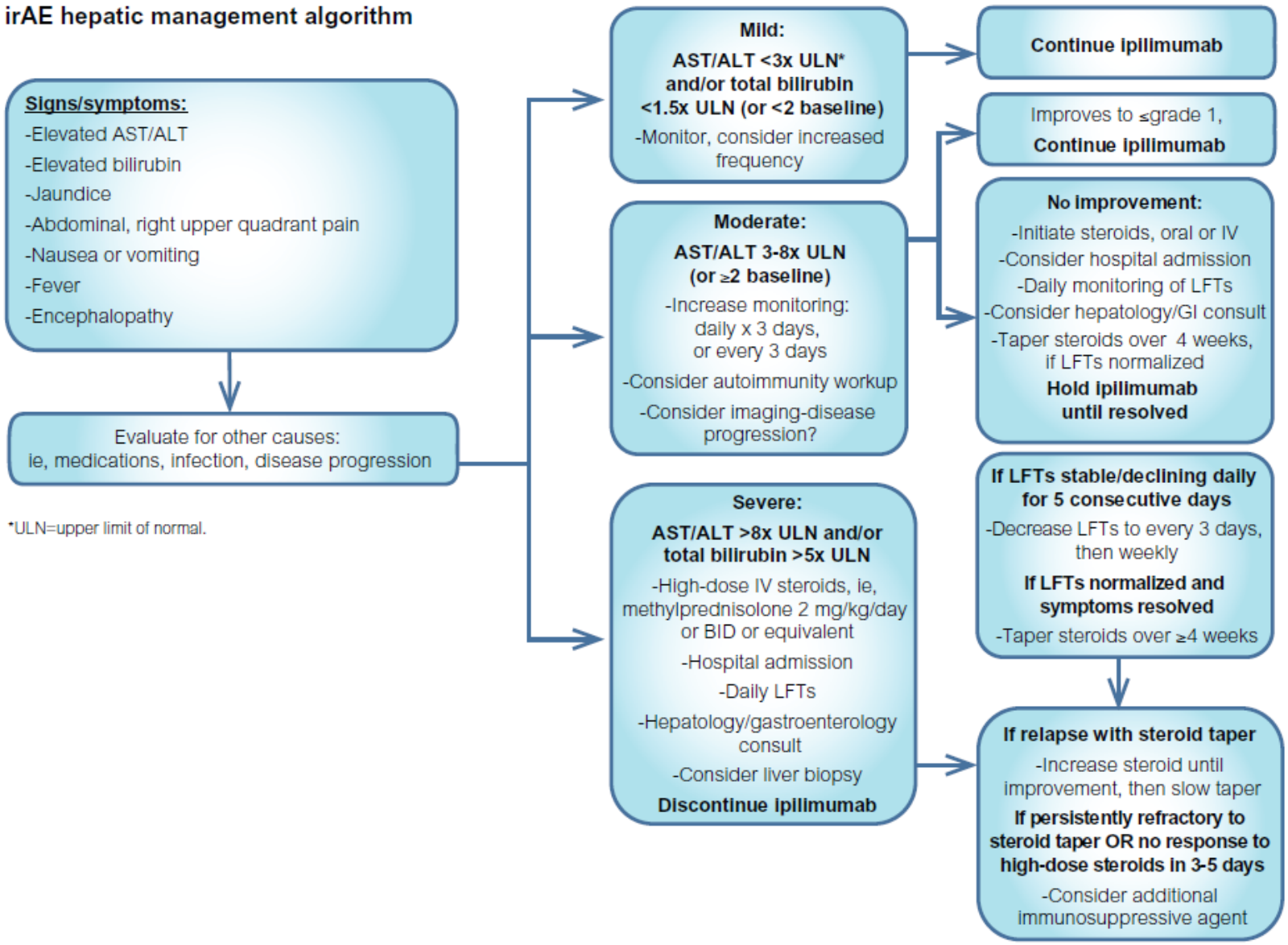
2. A clinical development paradigm for cancer vaccines and related biologics. Hoos A, Parmiani G, Hege K, Sznol M, Loibner H, Eggermont A, Urba W, Blumenstein B, Sacks N, Keilholz U, Nichol G; Cancer Vaccine Clinical Trial Working Group. J Immunother. 2007 Jan;30(1):1-15. Review.

3. Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria.Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbé C, Maio M, Binder M, Bohnsack O, Nichol G, Humphrey R, Hodi FS. Clin Cancer Res. 2009 Dec 1;15(23):7412-7420. Epub 2009 Nov 24.

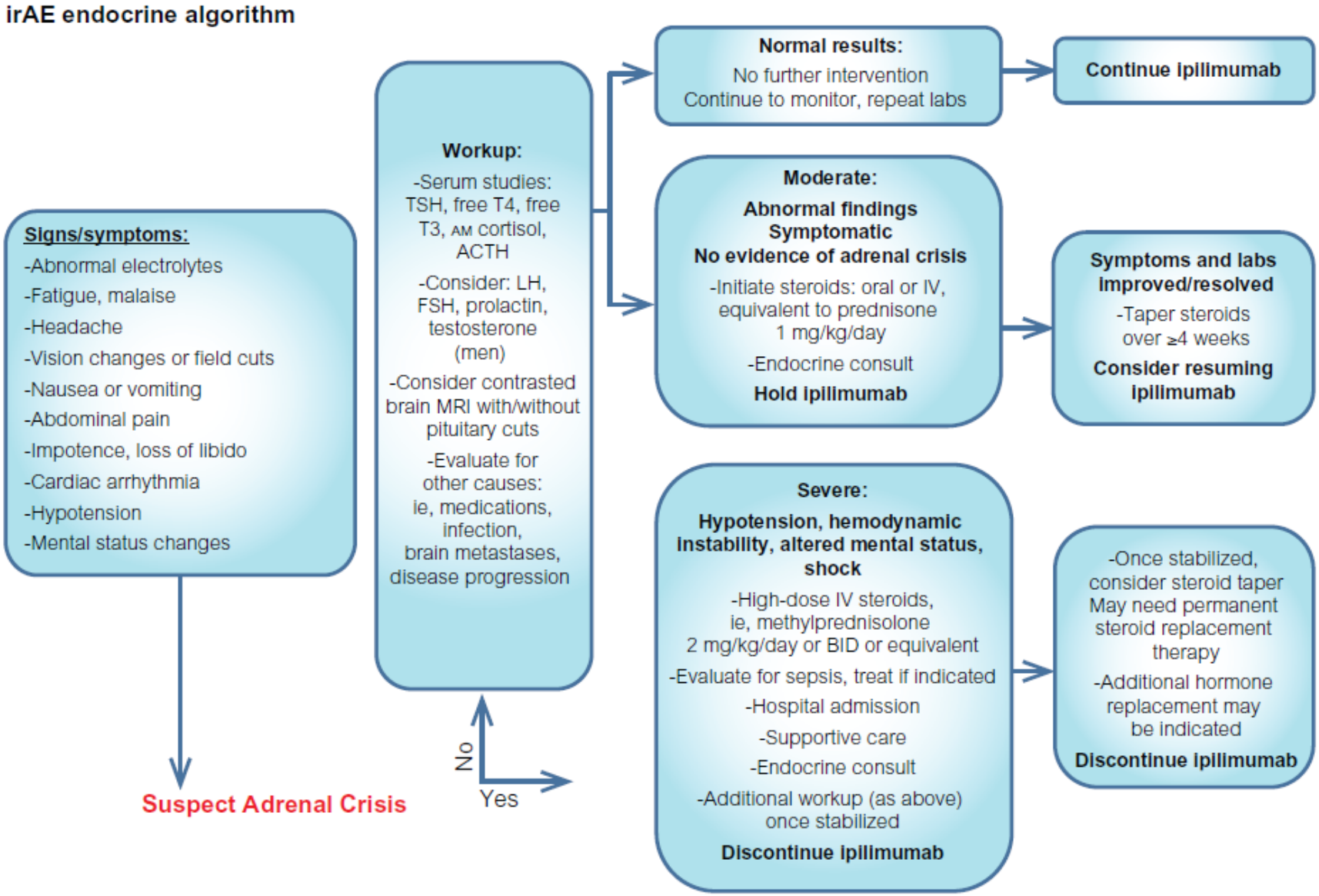
APPENDIX 5 – IRAE GASTROINTESTINAL MANAGEMENT ALGORITHM



APPENDIX 6 – IRAE HEPATIC MANAGEMENT ALGORITHM



APPENDIX 7 – IRAE ENDOCRINE ALGORITHM



APPENDIX 8 – NOVARTIS SAE FAX COVER SHEETS

NOVARTIS

Interventional Clinical Trial SAE Fax Cover Sheet

[redacted]

Investigator contact details:

Fax number : _____

Phone number : _____

Study Name	
Centre Number	
Patient Number	

Relationship between study treatment and event(s) is:

Suspected/Unknown

[redacted]

NOVARTIS

Interventional Clinical Trial SAE Fax Cover Sheet

[redacted]

Investigator contact details:

Fax number : _____

Phone number : _____

Study Name	
Centre Number	
Patient Number	

Relationship between study treatment and event(s) is:

Not Suspected

[redacted]