Official Title:	A Phase II Single Arm Study of High-Dose IL-2 and Ipilimumab in Patients With Unresectable Stage III and Stage IV Melanoma
NCT number:	02203604
Document Type:	Study Protocol and Statistical Analysis Plan; Informed Consent Form Main
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6.2.3 Treatment Visits

6.2.3.a Induction Treatment

Patients will have baseline blood tests and immune monitoring blood drawn prior to receiving study medications. Where indicated, a history and physical examination will also be done. Patients will receive ipilimumab (10 mg/kg) as described by intravenous injection over 90 minutes every three weeks for four total treatments. Any adverse events will be recorded.

For patients receiving ipilimumab in the out-patient setting, they will be admitted to the in-patient IL-2 unit on the same day as completing cycles 2 and 3 of ipilimumab. The patients should undergo routine screening for IL-2 as per institutional guidelines and begin treatment on the same evening as ipilimumab administration. IL-2 will be administered at 600,000 IU/kg every 8 hours per institutional guidelines.

6.2.4 Maintenance Treatment

Subjects will receive protocol therapy (a single 10 mg/kg IV dose given every 12 weeks) starting at week 24.

Follow-up Visits

6.2.5 Study Completion or Early Discontinuation Visit

At the time of study early withdrawal, the reason for early withdrawal and any new or continuing adverse events should be documented. The "Subject Off Study Form" should be completed.

6.2.6 Study Drug Discontinuation

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

6.2.7 Long Term Follow up

Patients will be followed up every 6 months by phone for survival status if patients are unable to visit the clinic.

6.3 Details of Procedures

6.3.1 Study Materials

[redacted] will provide ipilimumab at no cost for this study. IL-2 is commercially available.

[redacted]

All patients who receive at least one dose of ipilimumab will be considered evaluable for safety parameters. Additionally, any occurrence of nonserious or SAE from time of first drug administration, up to and including follow-up visits, will be reported. See Section 9: Adverse Event Reporting.

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

7. Criteria for Evaluation

7.1 Safety Evaluation

Refer to the NCI CTCAE, Version 4.0 (http://ctep.cancer.gov).

7.2 Efficacy Evaluation

7.2.1 Definition of Measurable/Non-Measurable and Index/Non-Index Lesions

Definitions of lesions are based on mWHO criteria

7.2.2 Definition of Measurable and Non-Measurable Lesions

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

7.2.2b **Non-Measurable (evaluable) Lesions** are all other lesions, including unidimensionally measurable disease and small lesions (lesions without at least one diameter ≥ 20 mm by conventional techniques), and any of the following:

- Lesions occurring in a previously irradiated area (unless they are documented as new lesions since the completion of radiation therapy), bone lesions, leptomeningeal

disease, ascites, pleural or pericardial effusion, lymphangitis cutis/pulmonis, abdominal masses that are not pathologically/cytologically confirmed and followed by imaging techniques and cystic lesions.

- All measurable and non-measurable lesions should be measured at screening and at the defined tumor assessment timepoints (see Section 5, Table 2). Extra assessments may be performed, as clinically indicated, if there is a suspicion of progression.

7.2.3 Definition of Index/Non-Index Lesions

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

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

7.2.4 Evaluation of Tumor Response Using mWHO Criteria

The mWHO criteria were developed as a hybrid tumor response classification system using elements of both the WHO and RECIST criteria in an attempt to more accurately measure tumor lesions and estimate tumor responses. Please see tumor measurement worksheet in Appendix

7.2.5 Definition of Index Lesion Response Using mWHO

Complete Response: Complete disappearance of all *index* lesions.

[redacted]

Partial Response: Decrease, relative to baseline, of 50% or greater in the sum of the products of the two largest perpendicular diameters of all *index* lesions.

Stable Disease: Does not meet criteria for complete or partial response, in the absence of progressive disease. Subject with PR or CR that is not confirmed after at least 4 weeks are scored as SD unless they have new primary lesions.

Progressive Disease: At least 25% increase in the sum of the products of all *index* lesions (taking as reference the smallest sum recorded at or following baseline) and/or the appearance of ***any*** new lesion(s).

7.2.6 Definition of Non -Index Lesion Response Using mWHO

Complete Response: Complete disappearance of all *non-index* lesions.

Stable Disease: A decrease or tumor stabilization of one or more *non-index* lesions. Subject with PR or CR that is not confirmed after at least 4 weeks are scored as SD unless they have new primary lesions.

Progressive Disease: Progression of *non-index* lesion(s) (e.g., an increase in pleural effusions, or other fluid collections defined as an approximate doubling of the volume which was present at baseline or nadir, unless there is radiographic evidence of a benign cause for the fluid collection or the effusion is cytologically negative for malignant cells).

7.2.7 Determination of Overall Response Using mWHO

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

Table 7 mWHO Response Criteria

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

[redacted]

Any	PD	Yes or No	**PD**
Any	**Any**	**Yes**	**PD**

Best OR is the best confirmed response designation over the study as a whole, recorded between the date of first dose until the last tumor assessment for the individual patient in the study. The assessment of response at 12 weeks has particular emphasis due to the mechanism of action of ipilimumab inducing immune responses as basis for clinical responses. For the assessment of best OR, all available assessments per patient are considered. CR, PR and PD determinations included in the best OR assessment must be confirmed by a second (confirmatory) evaluation meeting the criteria for response and performed no less than 4 weeks after the criteria for response are first met.

Imaging of the chest, abdomen and pelvis is required at screening (ie, baseline) and at each tumor assessment visit, regardless of the location of known metastases. Similar methods of tumor assessment and similar techniques must be used to characterize each identified and reported lesion at screening and during subsequent tumor assessments. Imaging-based evaluation is preferred to clinical examination.

If progressive disease is assessed based only on a new lesion(s) found on bone scans, additional imaging studies of the lesion(s) should be performed to confirm the malignant nature of the new findings on the bone scan. Increased intensity of uptake in previously abnormal areas on bone scans is not considered progressive disease, unless the lesions seen on the correlative imaging studies performed of this area meet the criteria for progression. New areas of abnormal uptake on a bone scan represent progressive disease.

8. INVESTIGATIONAL PRODUCT: IPILIMUMAB

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

Other medications used in the study as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, are considered noninvestigational products. In this protocol, non-investigational product(s) is/are: Interleukin-2 (IL-2, aldesleukin).

8.1 Identification

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

[redacted]
Approval Date: 08/2018
Expiration Date: 9/27/2018

8.2 Packaging and Labeling

BMS will provide ipilimumab at no cost for this study. Ipilimumab will be provided in open-label containers. The labels will contain the protocol prefix, batch number, content, storage conditions, and dispensing instructions along with the Investigational New Drug (IND) caution statement. Ipilimumab will be supplied at a concentration of 5 mg/mL in vials containing 40 mL solution.

8.3 Storage, Handling, and Dispensing

8.3.1 Storage

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

8.3.2 Handling and Disposal

As with all injectable drugs, care should be taken when handling and preparing ipilimumab. Whenever possible, ipilimumab should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents applying aseptic technique. Latex gloves are required. If ipilimumab concentrate or solution comes in contact with skin or mucosa, immediately and thoroughly wash with soap and water. After final drug reconciliation, unused ipilimumab solution should be disposed at the site following procedures for the disposal of anticancer drugs.

8.3.3 Dispensing

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

8.4 Drug Ordering and Accountability

8.4.1 Initial Orders

Following submission and approval of the required regulatory documents, a supply of ipilimumab may be ordered from [redacted]). The study PI (or delegate) must complete a Drug Request Form and email it to m[redacted] and [redacted] Please fax to [redacted] if you cannot send the form electronically.

[redacted]

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

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

8.4.2 Participating Sites

Participating sites should refer to the Pharmacy Manual for additional information on drug ordering, storage, accountability and destruction. For assistance with orders contact:

[redacted]

sey

[redacted]

- A completed R[redacted] Investigational Drug Request Form for a specific patient must be submitted for processing by 2pm EST. When additional supplies of the investigational agent are requested for a previously established patient, a copy of the Investigational Product Accountability Form must accompany the request for auditing purposes.

[redacted]

- Patient must be registered in Oncore® at [redacted]
- Ancillary sites should allow up to five (5) working days for delivery of IP to allow for internal processing and shipping via UPS next day air.
- The initial drug supply will be for the 4 doses of the induction phase. Future drug request will be limited to a twelve (12) week supply (2 maintenance doses) or less for each patient per order. To receive further drug supplies, a new Investigational Drug Request Form must be completed. When additional supplies of the IP are requested for a previously established patient, a copy of the DARF must accompany the request for auditing purposes.
- The shipping destination specified on the order form must be the same as the intended storage location for the transferred agent.
- A copy of the Investigational Agent Shipping Receipt accompanying the IP shipment must be returned ([redacted] to the [redacted]. The receiving site will note the date and person who received the IP. A copy of the form must be retained in the protocol drug accountability records. When additional supplies of the investigational agent are requested a copy of the DARF must accompany the request for auditing purposes.
- IP is not to be transferred or stored at any other location except the location specified on the request form and DARF.

8.5 Ipilimumab Accountability

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

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

8.6 Ipilimumab Destruction

If ipilimumab is to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for disposal and that procedures for proper disposal have

been established according to applicable regulations, guidelines, and institutional procedures. Appropriate records of the disposal must be maintained.

9. ADVERSE EVENT REPORTING

9.1 Collection of Safety Information

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

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.)

9.1.1 Serious Adverse Events

A ***serious adverse event (SAE)*** is any untoward medical occurrence that at <u>any dose</u>:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see note below for exceptions)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on 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 above. Examples of such events include but are not limited to intensive treatment in an emergency department or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

[redacted]

Additionally, 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 overdose, and cancer are not always serious by regulatory definition, these events must be handled as SAEs. Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as an SAE.

NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department for less than 24 hours that does not result in admission (unless considered an "important medical event" or a life-threatening event)
- elective surgery, planned before signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

Note that pregnancy in and of itself is not considered an SAE unless one of the above serious criteria has been met. However, all pregnancies, regardless of outcome, must be reported to Theradex® on a Pregnancy Report Form and followed to outcome, including pregnancies that occur in the female partner of a male study subject. **See Section 9.3.4 for instructions on reporting pregnancies.**

Note: Pregnancy Forms will be located in your study binders along with instructions.

9.1.2 Nonserious Adverse Events

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

9.2 Assignment of Adverse Event Intensity and Relationship to Investigational Product

[redacted]

The following categories and definitions of causal relationship to investigational product as determined by the investigator should be used:

- **Related:** There is a reasonable causal relationship to investigational product administration and the adverse event.
- **Not Related:** There is not a reasonable causal relationship to investigational product administration and the adverse event.

The expression "reasonable causal relationship" is meant to convey in general that there are facts (e.g., evidence such as dechallenge/rechallenge) or other arguments to suggest a positive causal relationship.

9.3 Collection and Reporting: AEs/SAEs

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

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

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

9.3.1 Serious Adverse Events

Following the subject's first administered dose of study treatment in the study, all SAEs, as defined in Section 9.1.1, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 90 days of discontinuation of dosing of the investigational product. If applicable, SAEs must be collected which relate to any later protocol-specified procedure (eg, a follow-up skin biopsy) or after 90 days if a causal relationship is suspected. [redacted] will notify BMS of any SAE occurring after this time period that is believed to be related to the investigational product or protocol-specified procedure.

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

[redacted]

Please refer to the SAE Report Form Completion Manual for instructions on completing the form.

Study sites should report all SAEs to [redacted] by email or fax to:

[redacted]

A copy of all SAEs will be forwarded by T[redacted], including the [redacted]

[redacted]

Serious adverse events, whether related or unrelated to investigational product, must be recorded on the SAE Report Form and submitted within 24 hours to Theradex® of site awareness of the event in order to comply with regulatory requirements. An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

All SAEs must be immediately reported by email (preferred) or fax . If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.) In selected circumstances, the protocol may specify conditions that require additional telephone reporting. If notification occurs to [redacted] by telephone, a completed SAE Report Form is expected within 24 hours.

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

[redacted]

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

9.3.2 Handling of Expedited Safety Reports

In accordance with local regulations, Theradex® will notify investigators of all SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the Investigator Brochure). In the European Union (EU), an event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of an expedited safety report (ESR).

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

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

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

9.3.3 Nonserious Adverse Events

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

If an ongoing nonserious AE worsens in its intensity, or if its relationship to the investigational product changes, a new nonserious AE entry for the event should be completed. Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for nonserious AEs that cause

interruption or discontinuation of investigational product, or those that are present at the end of study participation. Subjects with nonserious AEs at study completion should receive post-treatment follow-up as appropriate.

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

9.3.4 Pregnancy

Sexually active WOCBP must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized. Before enrolling WOCBP in this clinical study, the investigator must review the guideline about study participation for WOCBP which can be found in the GCP Manual for Investigators. The topics include the following:

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

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

All WOCBP MUST have a negative pregnancy test within 24hours before receiving ipilimumab. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG. If the pregnancy test is positive, the subject must not receive ipilimumab and must not be enrolled in the study.

In addition, all WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives(90 days after treatment) after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). The investigator must immediately notify Theradex® of this event and record the pregnancy on the Theradex® Pregnancy Report Form (not an SAE form) in accordance with the SAE reporting

[redacted]

procedures (refer to Section 9.3.1). Initial information on a pregnancy must be reported immediately to [redacted], and the outcome information provided once the outcome is known. The T[redacted] Pregnancy Report Form will be forwarded [redacted] for onward notification to [redacted]

Any pregnancy that occurs in a female partner of a male study participant should be reported to the Theradex® Safety Desk. Information on this pregnancy will be collected on the [redacted] Pregnancy Report Form.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator must report to T[redacted] as instructed above, follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome using the Theradex® Pregnancy Outcome Report Form. Infants should be followed for a minimum of 8 weeks.

9.3.5 Other Safety Considerations

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

10. STATISTICAL METHODOLOGY

Descriptive statistical will be used, except where otherwise specified. Continuous variables will be presented by summary statistics (such as mean, median, standard error and 90% CI) and the categorical variables by frequency distributions (i.e., frequency counts, percentages and 90% CI).

10.1 Sample size considerations

The primary goal of this clinical trial is to determine the clinical objective response rate within the first 24 weeks of ipilimumab and IL-2 in patients with unresectable Stage III and IV melanoma. Secondary endpoints include safety, feasibility, overall survival, one year and two year survival, progression-free survival, best overall response, and frequency of effector CD8+ T cells and CD4+FoxP3+ regulatory T cells.

[redacted]

For sample size calculations, we assume that objective response rate for ipilimumab alone is no greater than 14% and for IL-2 is no greater than 17%. Based on these assumptions, sample size calculations based on projected rates of response compared to ipilimumab and IL-2 alone are shown in Table 8. In order to detect a clinical objective response rate of 28% a sample size of 45 subjects are needed to show that the combination is better than ipilimumab alone and 82 subjects are needed to show improvement compared to IL-2 alone. Thus, we will seek to enroll 82 subjects. This results in 80% power to detect a meaningful response at alpha=0.05 and one-sided testing under one sample binomial distribution. If a 28% objective response rate is reached then the combination will be considered significant and further studies would be warranted.

It is anticipated that accrual will be at a rate of 5-10 patients per month and, thus, accrual should be completed within 12 months. We anticipate registration of 87-92 total patients to allow for patients who do not complete treatment with fully evaluable data.

Table 8. Sample size calculations for this clinical trial

Projected Rate of IPI+IL2 combination	Sample size needed to attain 80% power to compare with 14% rate for IPI alone	Sample size needed to attain 80% power to compare with 17% rate for IL2 alone
22%	n=134	N=373
25%	N=71	N=151
28%	N=45	N=82
30%	N=35	N=58

10.2 Patient Populations

The intent-to-treat (ITT) population is defined as all patients who have been registered to receive study treatment in this protocol. The PP population is defined as all patients who are eligible for the study and received at least two cycles of treatment.

10.3 Statistical Methods for Primary Objectives

The best objective response rate as determined by mWHO criteria at or before week 24 of treatment will be defined as the ratio of the number of patients whose best response is a CR

[redacted]

or PR divided by the total number of patients enrolled who have baseline and post-treatment assessments. Confirmation of responses requires a scan at least 4 weeks after the initial response and this may occur after the initial 24 week period. The analysis of this primary endpoint will be performed using exact one-sample binomial tests where the objective response rate of Ipilimumab and IL2 combination will be compared with published response rate of Ipilimumab alone and IL-2 alone. . The primary analysis will be done on the ITT population but a confirmatory analysis in the PP population will also be conducted. Patients will have formal documentation of their disease status at the week 12 and 24 imaging time point and the status of each patients response will be determined if they are withdrawn for any reason at the time of going off study.

10.4 Statistical Methods for Secondary Objectives

10.4.1 Secondary Efficacy Endpoints

Overall Survival (OS): This is defined as the time from the date of registration to the date of death from any cause. OS time will be censored at the last date the patient is known to be alive to the date of death; when the confirmation of death is absent or not known the date last known alive will be used. Patients are censored at the date of enrollment if no additional follow-up data are obtained. The median overall survival, survival at 1 year and survival at 2 and 3 years will be estimated using Kaplan-Meier method and their 90% confidence intervals will also be reported.

Progression-free Survival (PFS): This is defined as the time from the date of registration until the date of documented disease progression or death. This must be based on at least two imaging studies at least 4 weeks apart confirming disease progression. PFS will be based on the first documented imaging study to show disease response/progression based on mWHO guidelines. The PFS will be estimated using Kaplan-Meier method and the median PFS and its 90% confidence interval will be reported.

Best Overall Response Rate: The best overall response rate is determined by the study investigator once all the data for an individual patient is known during the treatment period. The best overall response is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on

last assessment has a best overall response of PR). The best overall response rate will be determined since some patients may exhibit delayed responses that occur after the week 24 assessment; therapeutic benefit for these patients would be captured by the best overall response and in survival data. A CR must be confirmed with a CT scan or appropriate imaging at 4 weeks. When SD is believed to be the best response, it must also meet the protocol specified time of initiating within 12 months of starting treatment and sustained for at least 12 weeks. For example, if a patient has SD at the 6 month assessment and PD at the 12 month assessment, the best response will be considered PD. Complete or partial responses may be claimed only if these assessments are confirmed at a subsequent time point at least 4 weeks later. The best overall response will be tabulated for all patients and the rate reported.

Disease control rate (DCR): The rate of patients who achieve a complete, partial or stable disease response will be determined by modified WHO criteria and recorded.

Safety and toxicity

A secondary objective of this study is to determine the safety and toxicity of ipilimumab in combination with IL-2. Safety assessments will include all treated patients receiving at least one dose of IL-2 or ipilimumab. Patients who are registered and withdraw from the trial before receiving any study treatment will be excluded from the safety analysis, but will be followed for response and survival. Safety assessments will be based on adverse events, laboratory data, concomitant medications, results of physical examinations and vital signs. An interim safety analysis will be conducted after the first 6 patients have completed four doses of ipilimumab. An independent DSMB will review the adverse events reported for these patients and make a determination to proceed with additional enrollment or to de-escalate the dose of ipilimumab at 3 mg/kg.

The type of toxicity occurring and their frequency and severity will be noted in intention-to-treat population. Adverse events will be listed by subjects within groups showing time of onset, period of event, grade classified using the CTCAE v.4.0, relationship to disease and outcome. If a patient experiences multiple events that can be linked to a single adverse event, the greatest severity and strongest investigator assessment of relation to study drug will be assigned that that adverse event. Since IL-2 and ipilimumab are both FDA approved

[redacted]

agents with defined toxicity profiles, the number of events in each classification of severity and relationship to treatment will be tabulated for each patient and summarized by treatment arm. This will allow detection of new or more sustained adverse events with the combination regimen.

10.4.2 Immune Responses

Evaluation of immunological responses will be primarily based on the breadth and magnitude of cellular responses (See Section 10 for more details). The frequency of tumor specific T cells and regulatory cells including CD4+ Tregs and effector CD8+ will be measured pre-treatment and various days post-treatment in the tumor and peripheral blood. Treatment effect for each patient will be measured as paired differences between pre and post measurements of these parameters at various times. Transformation of the data will be performed if appropriate, e.g. log transformation, and hence treatment effect will be expressed on a log scale. For further information on the statistical analysis of the immune responses see Section 10.7.

11. ADMINISTRATIVE SECTION

11.1 Compliance with the Protocol and Protocol Revisions

The study must be conducted as described in the final approved protocol. Documentation of approval signed by the chairperson or designee of the IRB(s) must be sent to the central protocol office before activating the study.

All revisions (protocol amendments, administrative letters, and changes to the informed consent) must be submitted to the central protocol office for submission to BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB of an Amendment, except where necessary to eliminate an immediate hazard(s) to study patients.

See also 21CFR for definitions of amendment and requirements.

- Investigators must follow all applicable requirements for protocol development, including 21 CFR 312.23(a)(6) and ICH Guidelines Part 6.
- See also 21 CFR 11, 50, 56, 312, and 314 for applicable Investigator/Sponsor information regarding study execution and conduct related to protocol requirements.

11.2 Informed Consent

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

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

11.3 Records and Reports

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 (e.g. medical record)) on each individual treated with Ipilimumab or entered as a control in the investigation. The investigator is required to retain, in a confidential manner, the data pertinent to the study.

11.4 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

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

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

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

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

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

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

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

11.6 Records Retention

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

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

12. Laboratory Studies

12.1 Collection of Samples for Immunology Assessment

Approximately 90 cc of peripheral blood will be collected at each time point indicated in Table 2 for immune monitoring. All specimens should have a "Specimen Submission Form" completed by the collecting research personnel and faxed to the central laboratory prior to shipping. Please refer to the Laboratory Manual for a more information.

Since immune assays and funding sources for immune monitoring are continuously evolving we will plan to store PBMC and serum for potential future immunologic assays, as appropriate.

Collection of Serum: For serum collection, whole blood will be collected in two red-top (no

[redacted]

additive) tubes. Immediately prior to drawing blood, the person in charge of the procedure will verify the subject's identity. Immediately after the blood has been collected, a label containing the appropriate subject identification number and the subject's initials is to be affixed to the vial. Serum will be stored for future studies to be determined by standards in the field and funding in the future.

Collection of PBMC: Whole blood (80 cc) will be collected in 4 green/red top CPT Tubestubes at the time points and in the quantities presented in Table 2. Prior to each blood draw, the patient's identity must be verified. Each vacutainer will be labeled with the patient's study identification number, initials, sample number, and the date the samples were taken.

HLA Typing: HLA typing will be determined by standard PCR analysis as previously described (83). Alternatively, HLA type can be determined by PCR-sequence specific oligonucleotides (PCR-SSOP) to resolve major allele groups to 4 digits, with some degeneracy e.g. HLA-A*23:01/03/05/06). In this case, genomic DNA from PBMC is amplified using PCR, then incubated with a panel of different oligonucleotide probes, which have distinctive reactivities with different HLA-types. The [redacted] will be used, where oligonucleotide probes are individually attached to up to 100 distinctly fluorescent microspheres. This allows the measurement of 100 different reactions in a single tube.

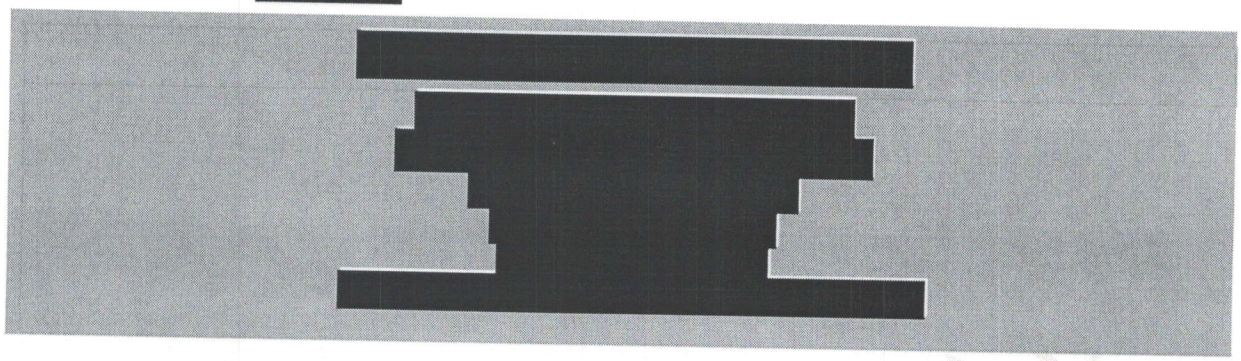
Tumor Biopsy (Optional) In selected patients tumor tissue may be obtained and submitted for analysis of the tumor microenvironment. Biopsy samples should be obtained under standard sterile surgical technique and placed into a sterile container. The container should be labeled with the patient's study identification number, initials, and the date the sample was taken.

Table 2: Immunology and Biomarker Sampling Schedule

Study Day	Time	Time relative to dosing	Serum	PBMC Flow cytometry	Tumor Tissue

		(Hours:mins)		(CD8+ Tcells, Tregs)	
Screening(-14 days to day 1)	Pre-dose	00:00	X	X	X (Once eligibility is determined)
Treatment Visit #1	Pre-dose	00:00	X	X	
Treatment Visit #2	Pre-dose	00:00	X	X	
Treatment Visit #3	Pre-dose	00:00	X	X	
Induction Assessment Follow-up #1	Pre-dose	00:00	x	X	
Follow-up #2: (Maintenance Treatment visit #5)	Pre-dose	00:00	X	X	
Follow-up #5(Maintenance Treatment visit #8)	Pre-dose	00:00	X	X	X
Follow-up(End of Treatment) #6	Pre-dose	00:00	X	X	X

Following the collection of whole blood or tumor tissue, the tubes/containers should be placed in the customized packaging systems and shipped directly to the core BRS Laboratory and ship to the following address:



Prior to shipping samples, the Laboratory Notification Form should be faxed directly to the lab at 7[redacted]. Blood samples cannot be shipped on Fridays or any day prior to a national holiday.

12.2 Tissue Processing

Specimens delivered to the lab will be handled and processed according to standard SOPs. Upon receipt of the Laboratory Notification Form an entry will be made and sample number issued for the expected sample in the Tumor Immunology Laboratory biospecimen repository database. Samples will be processed as follows:

Serum samples: Red top tubes will be centrifuged, with the samples being handled one subject at a time to avoid a mix-up. The serum will be divided into aliquots, by being transferred to the appropriate number of cryotubes previously labeled with self-adhesive labels that clearly identify the trial code, the patient number, the patient initials, and the visit number. The first tube (the primary sample) must be filled with at least 1 mL of serum. If only 1 mL or less is available, only one cryotube is to be used. Any remaining serum will be transferred to additional tubes (the retention samples) at 1.0 ml per vial. All tubes will be labeled with the patient study number and date. The serum will be kept frozen at --80 °C in a secure, locked freezer. The sample location will be recorded in the lab database. Refer to the Laboratory Manual for detailed instructions.

PBMC samples: CPT tubes will be processed to yield peripheral blood mononuclear cells (PBMC) in a distinct layer according to established protocol in the Tumor Immunology Laboratory. After collection and washing of the PBMC layer, cells will be counted, frozen,

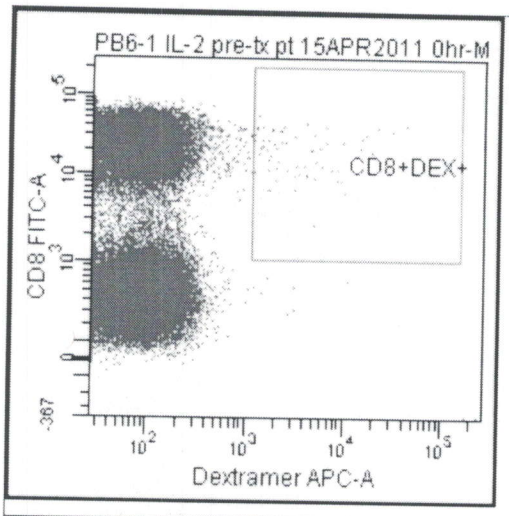
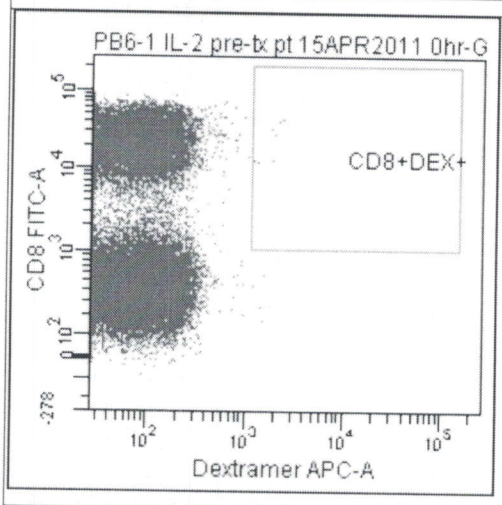
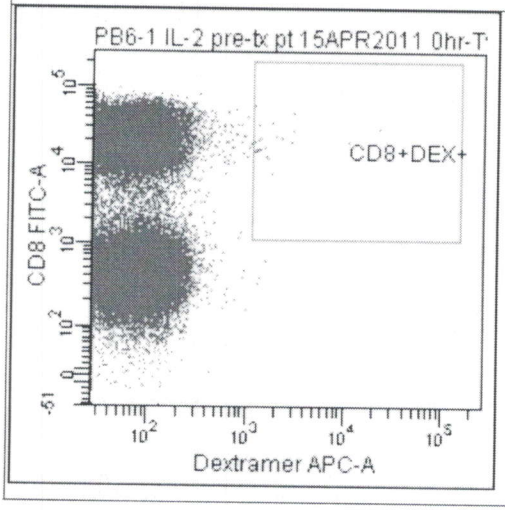
and stored in a secured liquid Nitrogen tank. All tubes will be labeled with the patient study number and date. The sample location will be recorded in the lab database. Refer to the Laboratory Manual for detailed instructions.

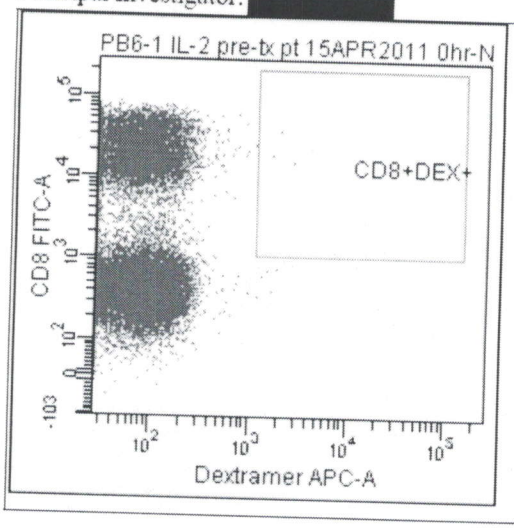
Tumor Biopsy: Fresh Tumors will be mechanically dispersed to yield single cell suspension according established protocol in the Tumor Immunology Laboratory. For the analysis of the melanoma antigen expression and local distribution pattern of immune cells by IHC and confocal microscopy, tumors will be also embedded in OCT solution and stored at -80°C. Samples will be stored in the liquid nitrogen freezer. Alternatively, paraffin blocks (preferred) or 20 unstained sections on adhesive slides from primary tumor and/or metastatic lesions (preferably both if available) for immunohistochemistry will be sent to the BRS Lab Laboratory. All tumor samples and/or patient blocks/slides will be labeled with the patient study number and date. The sample location will be recorded in the lab database. Refer to Laboratory manual for detailed instructions.

12.3 Immune Assessment

Determination of systemic immune responses

The development of systemic melanoma antigen specific T cell responses will be determined by dextramer staining using PBMC from patients and healthy donors (validation controls) separated by Ficoll density gradient centrifugation as described above Dextramer Assay. Human peripheral blood can be stained with MHC dextramers for selected melanoma antigens (MART-1, gp100, and tyrosinase) and controls (CMV, EBV). The staining procedure uses a CD8 antibody together with MHC dextramers (Immudex). Briefly, 100 µl whole blood is transferred to a 12 x 75 mm polystyrene test tube. 10 µl of the MHC dextramer is added and mixed with a vortex mixer. The tube is incubates in the dark for 10 minutes. A titrated amount of anti-CD8 antibody (Dako clone DK25) is added and mixed well. The mixture is incubated at 4°C in the dark for 20 minutes, Next, 2 ml EasyLyse working solution (Dako S2364) is added and the tube incubated for10 minutes. 2 ml 0.01 mol/L PBS is added and the tube is centrifuged for 5 minutes at 300 x g and the supernatant aspirated. The pellet is re-suspended in 0.4 ml PBS and analyzed by flow cytometry. An example of dextramer staining in the lab for MART-1, gp100, tyrosinase and no peptide (control) is shown in Figure 2 below.

	Patient was treated on a vaccine trial and whole blood was collected for CD8/dextramer analysis. This shows a positive response for **MART-1** dextramer.
	Patient was treated on a vaccine trial and whole blood was collected for CD8/dextramer analysis. This shows a negative response for **gp100** dextramer.
	Patient was treated on a vaccine trial and whole blood was collected for CD8/dextramer analysis. This shows a negative response for **tyrosinase** dextramer.



Patient was treated on a vaccine trial and whole blood was collected for CD8/dextramer analysis. This shows a negative control response with dextramer and **no peptide**.

Figure 2. Sample dextramer staining of peripheral blood from a single patient treated on an oncolytic vaccine trial. The flow cytometry demonstrated a "positive" MART-1 response.

If samples are available, some or all of the following analyses may also be performed:

Flow Cytometry Analysis: Phenotypic analysis for subtypes of T cells from tumor such as Tc, Th and Tregs will be analyzed by four color flow cytometry using FACSCaliber on leukocytes using the following antibodies (BD Biosciences): FITC conjugated anti-HLA class I and II, CD3, CD4, CD8; PE conjugated CD14, CD19, CD25, CD34, CD56, CD152, perforin, Granzyme B, CD107a, Foxp3; PE-Cy5 conjugated CD45 and APC-conjugated CCR7 and CD62L. For extracellular staining, cells will be incubated for 30 minutes at 4 C with optimal dilution of each Ab. Additional activation markers will also be evaluated, including HLA-DR, ICOS and PD-1.

Determine the cytokine profile of T cells: Th1 cytokines are associated with favorable responses while Th2 with progressive disease [81-82]. T cell subtypes are currently characterized *by their unique cytokine production; for Th1 we will use IL-2/IFN-γ; for Th2 we will use IL-4; for Th17 we will use IL-17 and for Ts/Treg cells we will use IL-10 and TGF-β [81-84]. The functional characteristics* of the T cells will be determined by their cytokine production profile, and we will sort 3 different subtypes: naïve, memory, Treg based on surface expression of CD45RA, CD62L, CCR7, CD25hi and CD127 Additional activation markers may be sought, including CD69, CD107a and PD-1.

Individual cell populations will be sorted and then stimulated with irradiated autologous or allogeneic DC pulsed with melanoma antigen peptide mixture for 2 days at 37oC, 5% CO2. Cells will be phenotyped for the intracellular cytokine production followed by Golgi Plug (Pharmingen) for 4 hours incubation prior to staining. For each marker, a corresponding isotype-matched mAb conjugated with the same fluorescent dye will be used as a negative control. This study will provide the data for dynamic changes of each subset of T cell populations during the immune responses.

Regulatory T cells: For the regulatory T cell population analysis, the following antibodies will be used: FITC-conjugated anti-CD4, -CD8, PE-conjugated anti-CD25, PE-Cy7-conjugated CCR7 and APC-conjugated CD45RA; APC-conjugated anti-CD4, PE-conjugated anti-CD25, intracellular APC-conjugated anti-Foxp3 and anti-GITR; PE-Cy7-conjugated anti-IL-10 and CyChrome7-conjugated anti-CD152 (all antibodies from BD Bioscience, San Jose, CA or eBioscience, San Diego, CA). Intracellular expression for FoxP3 will be detected using the Cytofix/Cytoperm kit (BD Biosciences), according to the manufacturer's instructions. MDSC, defined as CD14+CD11b+HLA-DR-/dim myeloid cells , which are enriched in tumor (our observation in human melanoma biopsies), will be stained with FITC-conjugated CD14, PE-conjugated HLA-DR, PerCp-ILT3 and APC-CD11b in addition to CD45-PE.6.5.

Treg Suppression Assay: Treg cells will be isolated with human CD4+CD25+ Regulatory T Cell Isolation Kit (Miltenyi, # 130-091-301) according to the manufacturer's recommendation. The purity of the cell population will be confirmed by flow cytometry and typically includes 85-95% for CD4+CD25+ T cells. All suppression assays will be performed in 96-well round-

[redacted]

bottom plates ([redacted]) in a final volume of 200 µl/well of DMEM + 10% heat-inactivated FCS (CellGro). The CD4+CD25- cells and the CD4+CD25 hi T cells will be plated at 3.0 × 104 cells/well at ratio of 1:1 – 1:20. Irradiated PBMCs will be added to all wells as APCs at 3.0 × 105/well. On day 6, 0.5 µCi of 3H-thymidine (PerkinElmer, Boston, MA) will be added for the final 16 hrs of culture. Cells will then be harvested on glass fiber filters and assessed for uptake of the labeled thymidine by liquid scintillation, as described previously [1]. This assay will be lower priority and done whenever sufficient cells are available.

12.4 Determination of the immune response in the tumor microenvironment

Immunohistochemistry and confocal microscopic analysis: Tumor samples will be stained for the expression of melanoma antigens and immune cells. In addition to hematoxylin and eosin staining, standard IHC using S100, HMB45 and tyrosinase staining will be done. For confocal microscopy, tumor tissue will be sectioned using a cryostat, sections will be fixed and incubated with Biotin- or FITC-conjugated anti-CD4, CD8, CD11c, CD68, CD83 (BD PharMingen), PE-conjugated anti FoxP3 (BD PharMingen). Biotin-stained samples will be then incubated with Cy5-conjugated streptavidin (Jackson ImmunoResearch). DAPI (Molecular Probes–Invitrogen) will be used to stain cell nuclei. Images will be obtained by using a confocal microscope.

Direct assessment of tumor infiltrating cells: To quantify the functional tumor specific CD8+ T cells ex vivo, tumor infiltrating T cells will be stained for intracellular cytokine staining in combination with HLA-restricted tetramers. The subsets of regulatory cells including Tregs, Ts, MDSC and cytotoxic effector CD8+CD107a+ T cells will be quantified by flow cytometry.

12.5 Statistical Analysis of Immune Responses

Data relating to immune response will be presented as descriptive summary statistics (such as mean, standard error and 90% CI). Immune response data will be summarized using number of subjects and percentages for categories as recorded as well as for classification of responder/non-responder. The major objective is first to determine the presence of activate CD8+ T cells and number of Treg cells. An increase in T cell precursor frequency greater than two-fold above the baseline is considered positive for tetramer/dextramer

[redacted] assays will be summarized using the empirical proportions, with exact 90% confidence intervals. In addition, a linear mixed effects model (treating patient effect as random) will be used to quantify the rise in immune responses (on a log scale) over time. The inter-assay variability is minimized in these assays by running the pre- and post-immunization samples at the same time. The intra-assay variability is determined by running all samples in triplicate or quadruplicate and the C.V has generally been below 20% for all assays (range 7-20%).

13. Human Subjects

13.1 Subject Population

This study is open to patients with metastatic melanoma who are 18 years of age or older and who may have received treatment of completely resected early stage melanoma, comprising interferon, radiation, or experimental vaccine therapy, and in the metastatic setting patients can have had treatment such as chemotherapy, immunotherapy (except prior treatment with Ipilimumab or IL-2), and other experimental agent.

13.2 Potential Risks

Patients will be receiving high-dose IL-2 and ipilimumab with risk profiles as described in Section 1. Patients will be asked to provide a tumor sample for analysis from a previous biopsy which would not involve any physical risks, or if there is melanoma that can be easily removed by a biopsy in the office, a sample will be taken. This biopsy is optional. Blood will be drawn for routine care and laboratory analysis associated with this protocol. There is a risk of discomfort, bruising and bleeding with the blood draws. Patients will also undergo imaging scans to determine the extent of their disease and their response to treatment that as part of their routine care. The risk of breach of confidentiality is minimal.

13.3 Consent Procedures

Informed consent must be obtained prior to commencing any research procedures. The PI shall seek such consent only under such circumstances that provide the prospective patient opportunity to consider whether or not to participate and that minimizes the possibility of coercion or undue influence. The information given to the patient, or the representative, shall be in a language understandable to the subject or representative. The informed consent document may not include any exculpatory language through which the subject or representative is made to waive any of the subject's legal rights or releases, or appears to release the investigator, the sponsor or the institution from liability for negligence.

[redacted]

[redacted]

13.4 Potential Benefits

It is possible that treatment with the combination of IL-2 and ipilimumab will have a therapeutic benefit, no benefit, or cause harm to the patient. Therefore, there is a potential for benefit to patients who participate in this study.

13.5 Risk-Benefit Ratio

Based on previous trials of IL-2 and ipilimumab, the NCI suggests that the combination is feasible and may be associated with meaningful therapeutic responses with a comparable rate of autoimmune toxicity. This clinical trial will be designed to better define the optimal dose and schedule of Ipilimumab with appropriate clinical follow-up to better determine the potential for combination treatment in melanoma. The overall risk-benefit ratio for patients entering this protocol is comparable to and possibly better than alternative options.

13.6 Gender and Minorities

No person shall, on the grounds of race, color, or national origin, be excluded from participation in, or be denied the benefits of, enrollment in this protocol.

14. Economic/Financial Considerations

This study is sponsored by Rutgers Cancer Institute of New Jersey with support from Bristol-Myers Squibb.

15. Publication of Research Findings

The policies and procedures of Rutgers University's legal department (see: Investigator's Handbook) will govern publication of the trial. It is expected that the results of this trial will be submitted for publication in a timely manner following the conclusion. The Cancer Institute of New Jersey PI, and all co-authors prior to submission or use, and designated BMS staff must review any abstract or manuscript.

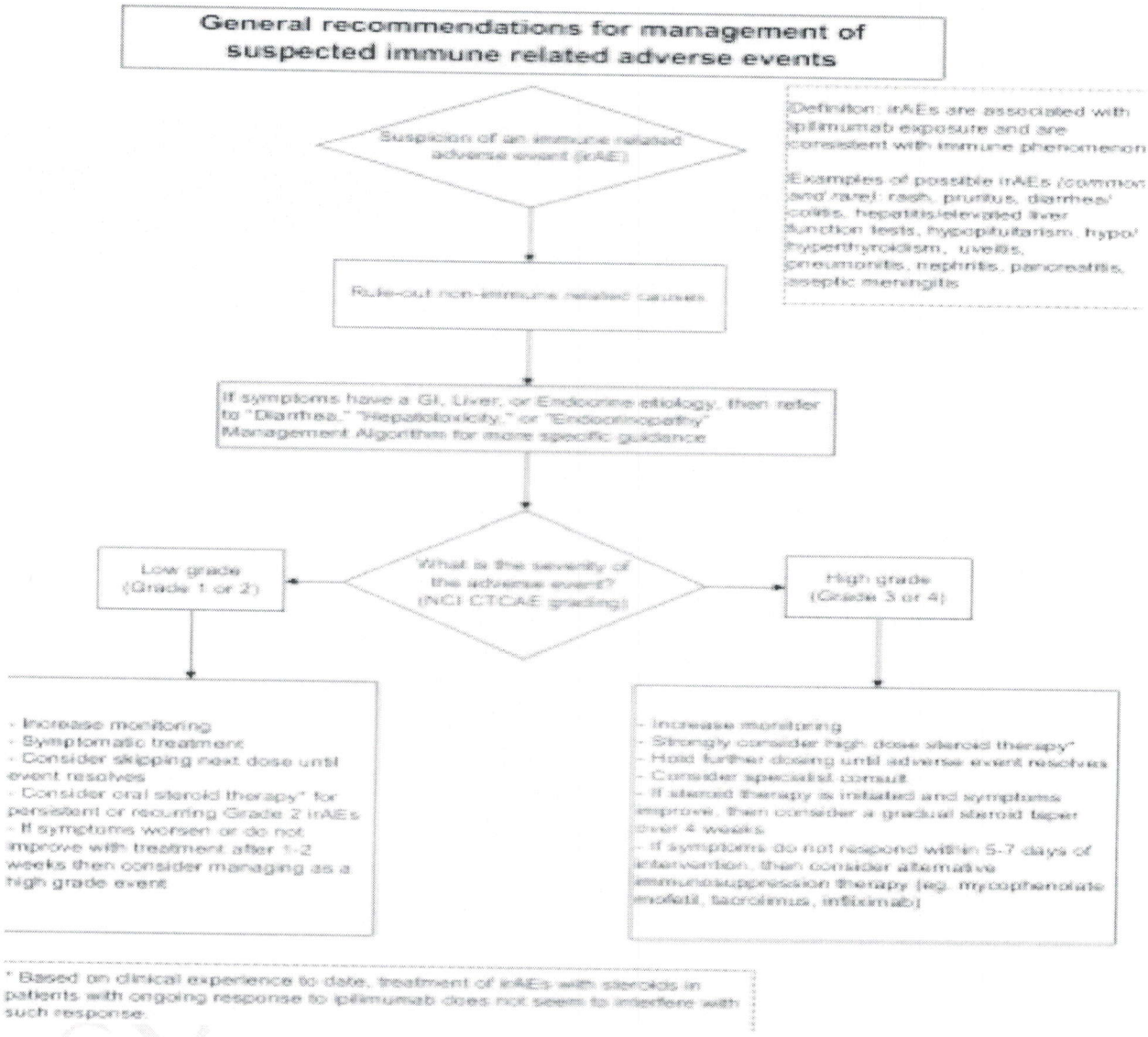
[redacted]

APPENDIX 1 LIST OF ABBREVIATIONS

Abbreviation	Term
ANC	Absolute Neutrophil Count
BID	Twice a Day
BMS	Bristol-Myers Squibb Company
CT scan	Computed Axial Tomography scan
CBC	Complete Blood Count
CR	Complete Response
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
ECOG PS	Eastern Cooperative Oncology Group Performance Status
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
irRC	Immune related response criteria
MRI	Magnetic Resonance Imaging
mWHO	Modified World Health Organization response criteria
PD	Progressive Disease
PFS	Progression Free Survival
PO	By Mouth
PR	Partial Response
QD	Once Daily
QoL	Quality Of Life
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SPD	Sum of the products diameters
SD	Stable Disease
TNM Staging	Tumor, Node and Metastasis Staging
TA	Tumor assessment

[redacted]

[redacted] RECOMMENDATIONS FOR IMMUNE-RELATED ADVERSE EVENTS (IRAES)



* Based on clinical experience to date, treatment of irAEs with steroids in patients with ongoing response to ipilimumab does not seem to interfere with such response.

[redacted]

[redacted]

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

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

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

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

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

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

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

Patients presenting with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have LFTs performed immediately and reviewed before administering the

[redacted]

next dose of study drug. Treating physicians should discuss, with the study PI, unexplained increases in LFTs $\geq$ 3 fold from baseline prior to any additional study drug administration.

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

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

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

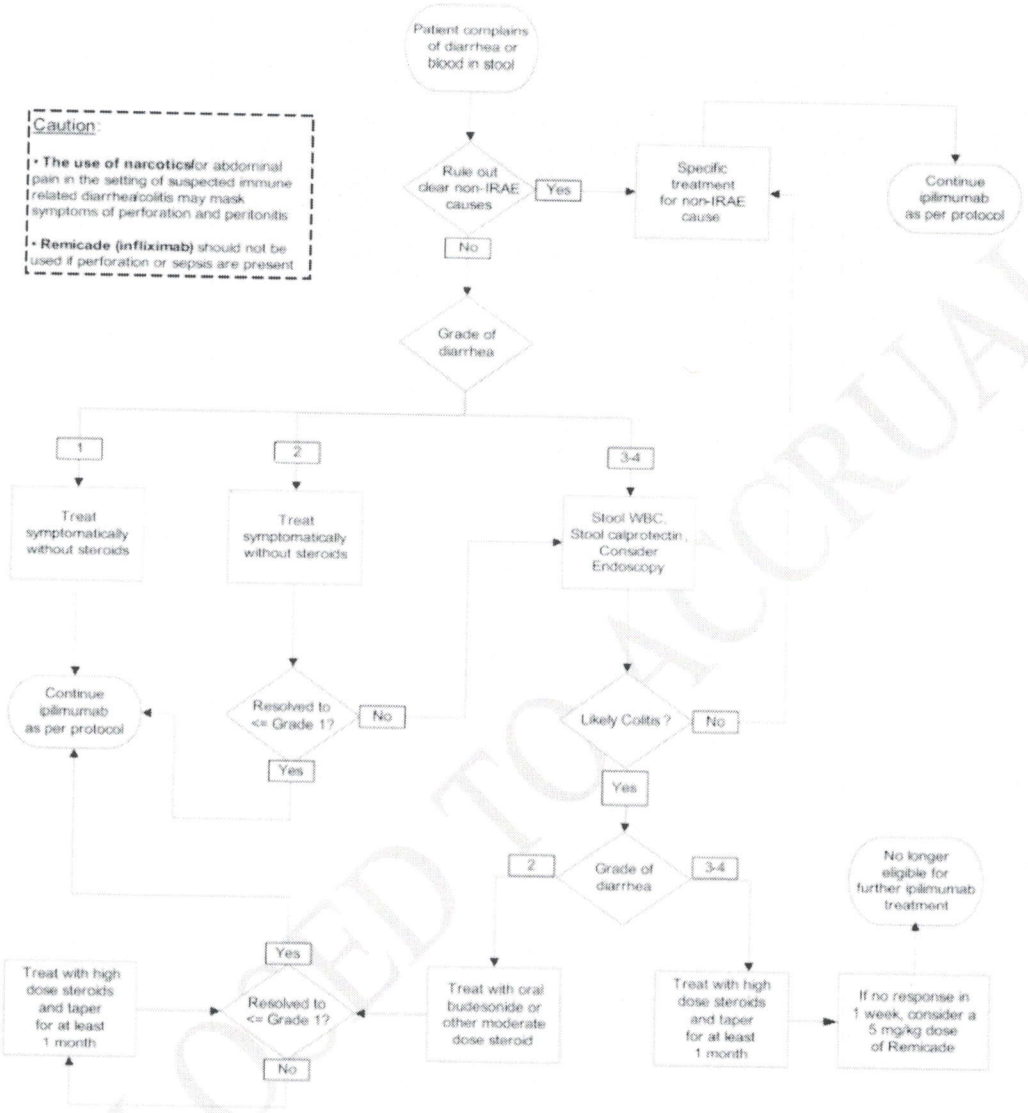
Endocrine: Patients with unexplained symptoms such as fatigue, myalgias, impotence, mental status changes, or constipation should be investigated for the presence of thyroid, pituitary or adrenal endocrinopathies. An endocrinologist should be consulted if an endocrinopathy is suspected. TSH and free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

Neuropathy: Patients should be monitored for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesias. Permanently discontinue YERVOY (ipilimumab injection) in patients with severe neuropathy (interfering with daily activities) such as Guillain- Barré-like syndromes. Institute medical intervention as appropriate for management of severe neuropathy. Consider initiation of systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent for severe neuropathies. Withhold YERVOY (ipilimumab injection) dosing in patients with moderate neuropathy (not interfering with daily activities).

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

[redacted]

APPENDIX 4 DIARRHEA MANAGEMENT ALGORITHM



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

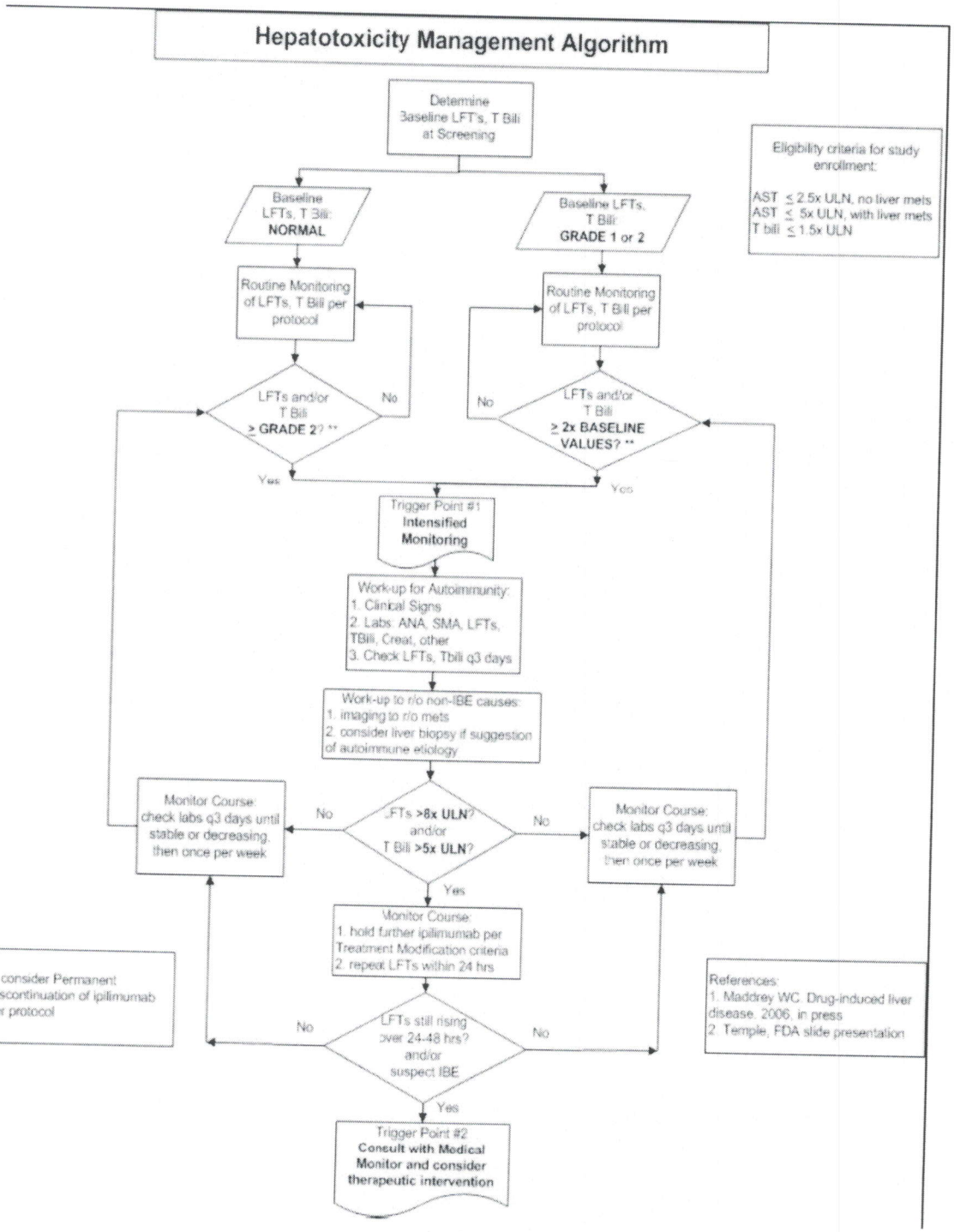
APPENDIX 5 HEPATOTOXICITY MANAGEMENT ALGORITHM

Situation: rising liver function tests (LFTs) > 8X ULN or suspected immune-mediated hepatitis. No mention of Bilirubin levels- What about the side effect of IL-2?)

1. Admit subject to hospital for evaluation and close monitoring
2. Stop further ipilimumab dosing until hepatotoxicity is resolved. Consider permanent discontinuation of ipilimumab per protocol (Section 6.2.5 of protocol)
3. Start at least 120 mg methylprednisolone sodium succinate per day, given IV as a single or divided dose
4. Check liver laboratory test values (LFTs, T-bilirubin) daily until stable or showing signs of improvement for at least 3 consecutive days
5. If no decrease in LFTs after 3 days or rebound hepatitis occurs despite treatment with corticosteroids, then add mycophenolate mofetil 1g BID per institutional guidelines for immunosuppression of liver transplants (supportive treatment as required, including prophylaxis for opportunistic infections per institutional guidelines)
6. If no improvement after 5 to 7 days, consider adding 0.10 to 0.15 mg/kg/day of tacrolimus (trough level 5-20 ng/mL)
7. If target trough level is achieved with tacrolimus but no improvement is observed after 5 to 7 days, consider infliximab, 5 mg/kg, once
8. Continue to check LFTs daily for at least 2 weeks to monitor sustained response to treatment

A flow chart of the algorithm is depicted in the following page.

[redacted]



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Approval Date: 1/8/2018
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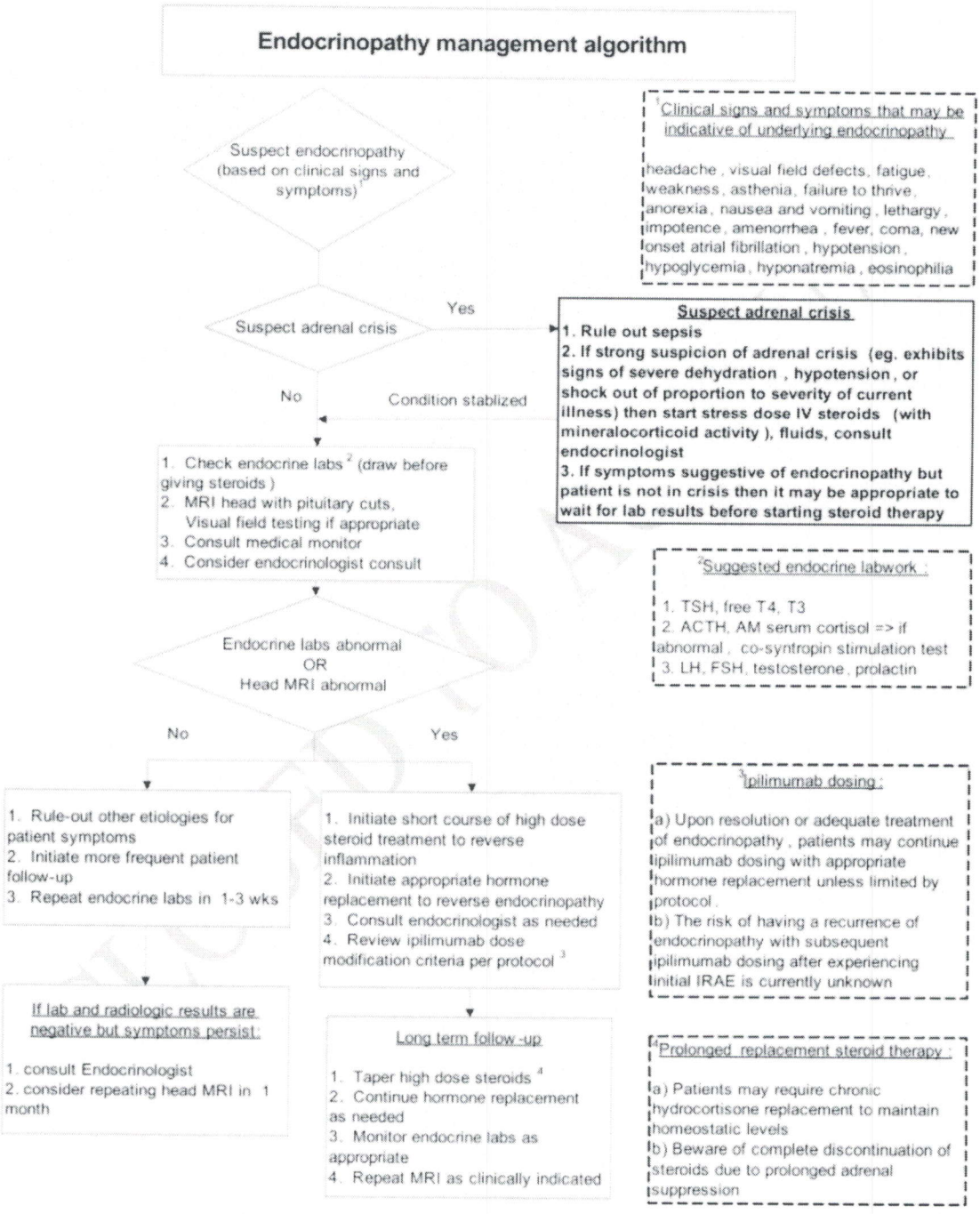
APPENDIX 6 ENDOCRINOPATHY MANAGEMENT ALGORITHM



Footnote
For numbered footnotes([1,2,3,4]), please refer to further explanation and text found in the corresponding dotted line boxes to the right side of the algorithm

[redacted]

SUBJECT REGISTRATION FORM

Protocol Number: CA184-084

Investigator Identification

Institution and affiliate name _____

Investigator's name _____

Investigator phone _____

Patient Identification

Patient's initials (Last, First) _____

Registration number _____

Patient demographics

Sex _____ M _____ F

Birth date (mm/yyyy) _____/_____

Race _____

Ethnicity _____

Prior therapy

_____

_____

_____

Informed Consent

Subject signed date (mm/dd/yyyy) ____/____/_____

Please attach a copy of the signed consent document to this form.

Pathology

Please attach a copy of the original pathology report to this form

PLEASE NOTE THAT SUBJECTS MUST MEET ALL OF THE ELIGIBILITY REQUIRMENTS LISTED IN SECTION 4.0 OF THE CLINICAL PROTOCOL

[redacted]

Please note that blood and tumor specimens must be submitted as detailed in Section 12 of the clinical protocol and using the **SPECIMEN SUBMISSION FORM located in the Laboratory Manual**.

SUBJECT ELIGIBILITY CHECKLIST

Protocol Number: CA184-084

[redacted]

Title: A Phase II Single Arm Study of High-Dose IL-2 and Ipilimumab in Patients with Unresectable Stage III and Stage IV Melanoma
Protocol Version Date: 03 Oct 2014
Protocol Number: CA184-084

Investigator Identification

Institution and Affiliate name: _____

Investigator's Name: _____

Investigator phone: _____

Participant Name: (Print First and Last)	Patient IWRS Screening Number:
Attending: (Print First and Last)	Consenting Professional : (Print First and Last)
Registering Individual: (Print First and Last)	Registering Individual Phone Number:
Date of Consent: ____/_____/_____	

Consent Questions:

1.0	Is the participant fluent in English? (Yes/No) *If Yes, skip to the Eligibility Criteria section; if NO, continue with Consent Question 2.0*	_____
2.0	What is the participant's primary language?_____	_____
3.0	Was an IRB-approved translated informed consent used in the participant's or legally authorized representative's primary language ?(YES/NO)	_____

[redacted]

4.0	Was an IRB-approved short-form given to the participant or legally authorized representative in their primary language? (YES/NO or NA)	_____
5.0	Was the IRB-approved English consent or summary signed by the consenting professional? (Yes/No/NA)	_____
6.0	Was an interpreter (non-family member or caregiver) used for the discussion? (YES/No/NA)	_____

The subject must meet the following criteria to be eligible for the trial (please check):

ELGIBILITY CRITERIA:

1.0	How old is the patient? (≥ 18 yes of age) DOB: ____/_____/_____ **Race** (Must circle AT LEAST one choice): American Indian/Alaskan Native Asian Black/African American White Native Hawaiian/other Pacific Islander **Ethnicity**(Must circle AT LEAST one choice): Hispanic Non Hispanic **Gender:** M/F	_____ _____ _____ _____
2.0	Does the patient have histologically or cytologically confirmed diagnosis of cutaneous melanoma that is considered unresectable (Stage III or IV) ? (YES/NO) Stage : T:_____N:_____M:_____ (Note: stage at study start) Date of Initial Diagnosis: ____/_____/_____	_____
2a.	Does the patient have Ocular or Mucosal melanoma? (No)	_____
4.0	Does the patient have measurable disease that is at least 20 mm by CT scan or ≥10 mm for spiral CT according to RECIST and WHO (mWHO) ? (Yes)	_____

5.0	Is the patient's life expectancy ≥ 3 months? (Yes)	_____
6.0	What is the patient's ECOG performance status? (0 or 1) Date: / /	_____
7.0	Is the patient accessible and able to comply with treatment, PK and immune-monitoring sample collection, and required study follow-up? (Yes)	_____
8.0	If the patient is a woman of childbearing potential (WOCBP), does she have a negative serum or urine pregnancy test (minimum sensitivity 25 UI/L or equivalent units of HCG) within 72 hours before the start of ipilimumab, or Day 1, which is acceptable per the sponsor ? (Yes/ NA- only if the patient is male or not of child bearing potential) Date: _____/_____/_____ If the woman is a women of NON-childbearing potential , please give reason for status: • Post –menopausal Date of last menstrual period: ___/_____/_____ • Hysterectomy and/or oophorectomy Date of surgery: ____/_____/___ • Other: Please explain: _____ ***Note: Non-childbearing potential is defined as:*** • Hysterectomy , bilateral tubal ligation, or bilateral oophorectomy • Amenorrhea ≥ 12 consecutive months without another cause and documented serum follicle stimulating hormone (FSH) level ≥40 mIU/ml • Irregular menstrual periods and a documented serum follicle stimulating hormone (FSH) level ≥40 mIU/ml and Receiving hormone replacement therapy (HRT) ***Note: FSH level testing is not required for women ≥ 62 years old with amenorrhea of > 1 year.***	_____

9.0	If the patient is a WOCBP, does she agree to use an acceptable method of contraception to avoid pregnancy throughout the study and for at least 4 weeks prior to initiation of drug and for at least 26 weeks after the last dose of investigational product in such a manner that the risk of pregnancy is minimized? (Yes/ NA –only if the patient is male or not of childbearing potential)	
10.0	If the patient is a sexually active male, does he agree to use an acceptable method of contraception throughout the study and for at least 4 weeks prior to initiation of the drug and for at least 8 weeks after the last dose of investigational product in such a manner that the risk of pregnancy is minimized? (Yes/NA-only if the patient is a female)	
11.0	Is the patient pregnant or breastfeeding? (No/NA-only if the patient is a male)	
12.0	Does the patient have known or suspected brain metastasis? (Yes/NO)	
13.0	**If Yes to 12.0,** have the brain metastases been previously treated? (Yes/NA- only if the answer to question 14.0 is No)	
14.0	**If Yes to 12.0,** has an MRI with and without contrast or CT of the brain been performed to rule out brain metastases or to show no evidence of progression for at least 4 weeks? (Yes/NA-only if the answer to question 14.0 is No)	
15.0	**If Yes to 12.0**, has the patient been off immunosuppressive doses of systemic medications, at least 4 weeks at time of enrollment? (Yes/NA-only if answer to question 14.0 is No) Note: Corticosteroids have a washout period of 14 days prior to randomization.	
16.0	Does the patient have prior malignancy active with the previous 5 years? (No)	

[redacted]

17.0	Does the patient have any active autoimmune disease or a documented history of autoimmune disease? (No)	_____
18.0	Does the patient have a history of a syndrome that required systemic steroid or immunosuppressive medications? (No) Note: Subject with vitiligo , psoriasis in active within the past 2 years , resolved childhood asthma/atophy , or thyroid disease controlled by replacement therapy without the need for immunosuppression are eligible	_____
19.0	Does the patient have known or suspected human immune deficiency virus (HIV) , hepatitis B or C infection? (No)	_____
20.0	Does the patient have or a history of extensive pulmonary metastases or chronic pulmonary disease history? (No) Date: _____/_____/_____ Note: FEV1 and FVC > 65% Note: Only for patients with pulmonary function: FEV1 and FVC > 65% of prediction for those patients with extensive pulmonary metastases or chronic pulmonary disease history.	_____
22.0	Is the patient on beta-blockers? (Yes/No) *Note: Patients may be weaned off of beta-blockers two weeks prior to study enrollment under the supervision of their primary cardiologist.*	_____
23.0	Does the patient have an underlying heart condition and those 50 years or older who have reversible ischemic changes on cardiac stress test who are deemed ineligible for surgery by cardiology consult? (No) Date of Cardiac Stress Test: _____/_____/_____	_____
24.0	Has the patient been treated with IL-2, ipilimumab or prior CTLA-4 inhibitor or agonist? (Yes/No) Note: not for metastatic disease.	_____
25.0	If yes to 26.0, has it been at least 6 months since the final adjuvant treatment from start of study treatment?	_____

[redacted]

	(Yes/NA only if answered NO to 26.0) Date: _____/_____/_____	
26.0	If yes to 26.0 did the patient have Grade 3 or greater adverse events with prior adjuvant ipilimumab therapy that did not resolve with limited corticosteroid use? (No/ NA only if answered NO to 26.0)	[redacted]
27.0	Does the patient have presence of an 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 ? (No)	[redacted]
28.0	Does the patient have evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, ECG or clinical laboratory determinations beyond what is consistent with the target population? (No)	[redacted]
29.0	Has the patient been treated with systemic anti-cancer treatment (including investigation drugs) within 4 weeks of first dose of study medication? (No) Date of Last Treatment: _____/_____/_____	[redacted]
30.0	Has the patient been treated with immunosuppressive medications or immunosuppressive doses of systemic corticosteroids (doses ≥ 10 mg/dcay prednisone or equivalent) within 14 days of first dose of study medication? (No)	[redacted]
32.0	Did the patient have surgery or radiotherapy within 4 weeks prior to enrollment without any sequelae of the enrollment of study medication? (No)	[redacted]
33.0	Did the patient have any non-oncology live viral vaccine therapies used for prevention of infectious disease within 1 month of the first dose of study medication? (No)	[redacted]
34.0	Did the patient have prior treatment with Ipilimumab	[redacted]

	or IL-2? (No)	
35.0	Has the patient been treated with anti-CTLA 4? (No)	_____
36.0	Is the patient a prisoner or involuntarily incarcerated? (No)	_____
37.0	Is the patient compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness? (No)	_____
38.0	What is the patients ANC? (≥ 1000/uL) Date: _____/_____/_____	_____
39.0	What is the patient's platelet count? (≥ 75,000 /uL) Date: _____/_____/_____ ***Note: Transfusion to achieve the required levels respectively is not permitted.***	_____
40.0	What is the patient's Hemoglobin? (≥ 9.0 g/dL) Date: _____/_____/_____ ***Note: (≥ 80 g/L; may be transfused)***	_____
41.0	What is the patient's total creatinine? (≤ 2.0 x ULN) Date: _____/_____/_____	_____
42.0	What is the patient's total bilirubin? (≤ 2.0 x ULN) Date: _____/_____/_____ Does have patient Gilbert's Syndrome? (Yes/No) Note: patients with Gilbert's Syndrome, who must have a total bilirubin less than 3.0 mg/dL)	_____ _____ _____
43.0	What is the patient's AST? (≤ 2.5 x ULN for patients without liver metastasis, ≤ 5 times for patients with liver metastases) Date: _____/_____/_____	_____
44.0	What is the patient's ALT? (≤ 2.5 x ULN for patients without liver metastasis, ≤ 5 times for patients with liver metastases) Date: _____/_____/_____	_____
45.0	Is the patient willing and able to provide signed informed consent, including consent for any screening procedures conducted to establish eligibility for registration, required prior to trial participation? (Yes)	_____

[redacted]

[redacted] Team (Physician or Consenting Professional)

Reviewed and Approved by : (Print First and Last Name)	Title:
Reviewed and Approved by: (Signature)	Date: _____/_____/_____
By signing above I attest that I have reviewed and confirmed that the above eligibility has been met	

External Registration Instruction Section	
1.0	**Registration will be performed by Theradex's IWRS System** ____/____/___ Patient Identification Patient's initials (Last, First) _____ IWRS Screening Number _____

Pre-Treatment Evaluation:		
	TO BE COMPLETED WITHIN 1 MONTHY OF STUDY DRUG ADMINISTRATION	
1.0	Informed Consent	____/____/____
2.0	Medical History including toxicities or allergy related to previous treatments	____/____/____
3.0	ECOG Performance Status	____/____/____
4.0	Complete Physical Examination	____/____/____
5.0	Concomitant Medication Review (Checking for protocol-excluded medications)	____/____/____
6.0	Clinical Complaints and Adverse Events	____/____/____
7.0	CT/MRI of chest, abdomen and pelvis (w/w/o contrast)	____/____/____
8.0	CT/MRI of Brain (w/w/o contrast)	____/____/____
9.0	Cardiac Stress Test	____/____/____
10.0	Pulmonary Function Test(if needed)	____/____/____

[redacted]

[redacted]

TO BE COMPLETED WITHING 2 WEEKS OF STUDY DRUG ADMINISTRATION		
11.0	Fresh Tumor Biopsy (optional)	/ /
12.0	Biochemistry-Electrolytes (sodium, potassium, calcium, chloride and magnesium, serum creatine, BUN)	/ /
13.0	Phosphorous	/ /
14.0	ALT/AST/ALP, Total Bilirubin (Hepatic Function)	/ /
15.0	Hematology(CBC w/ Differential , Platelets)	/ /
16.0	T3,TSH,T4,	/ /
17.0	LDH	/ /
18.0	12- Lead ECG	/ /
19.0	Serum Protein	/ /
20.0	Albumin	
21.0	Urinalysis	/ /
22.0	Vital Signs Temp:_____BP:_____Respiratory Rate:_____ Heart Rate:_____; Height: ;Weight:_____	/ /
TO BE COMPLETED WITHIN 72 HOURS OF Study Drug ADMINISTRATION		
24.0	Pregnancy Test (Serum)- if applicable Note: Day 1 is OK	/ /

[redacted]

[redacted] OFF STUDY FORM

Protocol Number: A Phase II Single Arm Study of High-Dose IL2 and Ipilimumab in Patients with Unresectable stage III and Stage IV Melanoma.
Protocol [redacted] CA -184-084. [redacted]

Investigator Identification
Institution and affiliate name _____
Investigators name _____

Patient Identification
Patient's initials (Last, First) _____
Registration number _____

Date Subject is Off Study (mm/dd/yyyy) ____/____/_____

Reason Subject is Off Study:
_____ best response achieved; date ____/____/_____
_____ progressive disease; date ____/____/_____
_____ toxicity; describe
_____ lost to follow-up
_____ physician preference
_____ patient withdrawal; reason
_____ patient never received tx; reason
_____ other; describe

_____
Investigator Name (print)

_____ _____
Signature of Investigator Name Date

[redacted]

[redacted]

ECOG performance status table:

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

Karnofsky Performance Status (KPS) to ECOG Conversion Table:

KPS	ECOG
100	0
90	1
80	1
70	2
60	2
50	3
40	3
30	4
20	4
10	4
0	5

Karnofsky Performance Status
(D.A. Karnofsky and J.H. Burchenal, The clinical evaluation of chemotherapeutic agents in cancer. In: C.M. MacLeod, Editor, Evaluation of chemotherapeutic agents in cancer, Columbia University Press, New York (1949), pp. 191-205).

- 100%- normal, no complaints, no evidence of disease.
- 90%- Able to carry on normal activity, minor signs or symptom of disease.
- 80%- Normal activity with effort, some signs or symtoms of disease.
- 70%- Cares for self, unable to carry on normal activity or to do work.
- 60%- Requires occasional assistance from others but able to care for most needs.
- 50%- Requires considerable assistance from others and frequent medical care.
- 40%- Disabled, requires special care and assistance.
- 30%- Severly disabled, hospitalization indicated, death not imminent.
- 20%- Very sick, hospitalization necessary, active supportive treatment necessary.
- 10%- Moribound, fatal processes progressing rapidly.
- 0%-Dead.

Tumor Assessment Form:

RECIST 1.1: BI-DIMENSIONAL RESPONSE ASSESSMENT FORM (WHO)

Protocol #:			Disease:					
TARGET LESIONS								
Target Lesion #	Organ (maximum 10 target lesions & 5 per organ)	Series/Image at Baseline	Baseline Date: ☐ sent to EMR for scanning	Follow-up #: Date: ☐ sent to EMR for scanning		Follow-up #: Date: ☐ sent to EMR for scanning		Follow-up #: Date: ☐ sent to EMR for scanning	
	SCAN TYPE: CT:CAP, Brain MRI		Diameter(mm)	Series/Image	Diameter(mm)	Series/Image	Diameter(mm)	Series/Image	Diameter(mm)
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
				From baseline	From nadir	From baseline	From nadir	From baseline	From nadir
		SUM	N/A						
		% change							
Overall Response of Target Lesions				☐CR ☐PR ☐SD ☐PD		☐CR ☐PR ☐SD ☐PD		☐CR ☐PR ☐SD ☐PD	
NON-TARGET LESIONS									
Non-Target Lesion #	New Lesions (check if applicable)	Organ and location							
1	☐		☐ Pres	☐ Pres ☐ Abs ☐ PD		☐ Pres ☐ Abs ☐ PD		☐ Pres ☐ Abs ☐ PD	
2	☐		☐ Pres	☐ Pres ☐ Abs ☐ PD		☐ Pres ☐ Abs ☐ PD		☐ Pres ☐ Abs ☐ PD	
3	☐		☐ Pres	☐ Pres ☐ Abs ☐ PD		☐ Pres ☐ Abs ☐ PD		☐ Pres ☐ Abs ☐ PD	
4	☐		☐ Pres	☐ Pres ☐ Abs ☐ PD		☐ Pres ☐ Abs ☐ PD		☐ Pres ☐ Abs ☐ PD	
5	☐		☐ Pres	☐ Pres ☐ Abs ☐ PD		☐ Pres ☐ Abs ☐ PD		☐ Pres ☐ Abs ☐ PD	
6	☐		☐ Pres	☐ Pres ☐ Abs ☐ PD		☐ Pres ☐ Abs ☐ PD		☐ Pres ☐ Abs ☐ PD	
Overall Response of Non-Target Lesions				☐CR ☐SD ☐PD		☐CR ☐SD ☐PD		☐CR ☐SD ☐PD	
OVERALL RESPONSE				☐CR ☐PR ☐SD ☐PD		☐CR ☐PR ☐SD ☐PD		☐CR ☐PR ☐SD ☐PD	

Target lesions (the min. size of a measurable lesion must be at least double the slic
-non-nodal must be: LD ≥ 10 mm on CT/MRI
-measurable lymph nodes must be ≥ 15 mm in the short axis on CT/MRI
-clinically must be ≥ 10 mm when measured with calipers

Response of target lesions

CR: Disappearance of all target lesions. lymph nodes must be < 10 mm short axis
PR: At least a 30% decrease in the sum of diameters
PD: At least a 20% increase in the sum of diameters
SD: Neither PR nor PD.

Non-Target lesions : All other lesions, including sma l lesions (LD <10mm or pe

Response of non-target lesions

CR: Disappearance of all non-target lesions and normalisation of tumour mark
Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or ma
PD: Progression of existing non-target lesions/new lesions

Evaluation of best overall response

Target lesion	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/ non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
PD	Any	Yes or No	PD

SUMMARY FOR BEST OVERALL RESPONSE

Best Overall Response _____ PI Signature (confirmation of summary responses): _____

Date of Best Overall Response _____ Date: _____

Date of Progression _____ Comments (if any changes have been made to prior measurements, please explain): _____

THIS DOCUMENT MUST BE SCANNED INTO THE EMR AFTER EACH ASSESSMENT

Page____ ☐ Check if final assessment

[redacted]

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Approval Date: 1/8/2018
Expiration Date: 9/27/2018

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