Memorial Sloan Kettering Cancer Center
IRB Number: 16-043 A(11)
Approval Date: 25-Jun-2018

PARKER INSTITUTE
for CANCER IMMUNOTHERAPY

FINAL CLINICAL STUDY PROTOCOL

Protocol Number: PICI0001
Protocol Title: A Randomized, Phase 2 Study of Ipilimumab vs Ipilimumab plus Nivolumab in Patients with Stage III-IV Melanoma Who Have Progressed or Relapsed on PD-1 Inhibitor Therapy

IND Number:	Not Applicable
Name of Product:	Ipilimumab and Nivolumab
Phase of Development:	2
Indication:	Stage III-IV Melanoma
Sponsor:	Parker Institute for Cancer Immunotherapy 1 Letterman Drive, Suite D3500 San Francisco, CA 94129 Tel: 415-985-7311 Fax: (415) 872-5305
Protocol Version:	3.0
Protocol Date:	06 March 2018

Document History

Document	Change	Changes To The Protocol	Rationale for Change
Original Protocol 23 Aug 2016	**NA**	**NA**	**NA**
Final Protocol 28 Sept 2016 (Location in Protocol Version 1.0, dated 19 Sept 2016)			
Title page	Addition of text and figure	• Sponsor address was added in the updated protocol • Sponsor logo was added	To complete required information on title page of new protocol template
Sponsor approval page	Addition of text	Sponsor signatory details were added	
Investigator protocol agreement page	Addition of text	Required text and Principal Investigator's details were added	
Section 1, Synopsis	Section created	Developed protocol synopsis based on information presented in the updated protocol body text	Section required per new protocol template
Various sections in the protocol	Transfer of text	Complete text from previous protocol was transferred to the new protocol template under various headings and subheadings	To adopt new protocol template
Section 7.5, Follow-Up for Drug Discontinuation/Participant Withdrawal from Study	Addition of text	If a participant discontinues study treatment and is withdrawn from the study for any reason, the study site must immediately notify the medical monitor. The date and the reason for study discontinuation must be recorded on the electronic case report form (eCRF). Participants who withdraw prematurely are to attend an Early Termination Visit, if possible, and complete all assessments. In the event that a participant discontinues prematurely from the study due to a treatment-emergent adverse events (TEAE) or serious TEAE, the TEAE or serious TEAE will be followed until it resolves (returns to normal or baseline values) or stabilizes, or until it is judged by the Investigator to be no longer clinically significant. Once a participant is withdrawn from the study, the participant may not re-enter the study.	Text included in the updated protocol based on required section heading in new protocol template

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Section 8.6, Treatment Accountability and Compliance	Addition of text	Administration of study drugs will be supervised by study personnel or assigned infusion room nursing staff, who will monitor compliance. Study drugs accountability will be maintained in the Pharmacy Source documents i.e. accountability logs or in the study master file, as required.	Text included in the updated protocol based on required section heading in new protocol template
Section 9.2.4, Unscheduled Visits	Addition of text	The Investigator may at his/her discretion arrange for a participant to have an unscheduled assessment, especially in the case of AEs that require follow-up or an AE considered by the Investigator to be possibly related to the use of study drug. The unscheduled visit page in the eCRF must be completed.	Text included in the updated protocol based on required section heading in new protocol template
11.5.3, Pregnancy	Addition of text	Female participants of child-bearing potential must have a negative pregnancy test at Screening. Following administration of study drug, any known cases of pregnancy in female participants will be reported until the participant completes or withdraws from the study. The pregnancy will be reported immediately by phone and by faxing/emailing a completed Pregnancy Report to the Sponsor (or designee) within 24 hours of knowledge of the event. The Investigator will follow the participant until completion of the pregnancy and must assess the outcome in the shortest possible time but not more than 30 days after completion of the pregnancy. The Investigator should notify the Sponsor (or designee) of the pregnancy outcome by submitting a follow-up Pregnancy Report on a Pregnancy Surveillance Form. If the outcome of the pregnancy meets the criteria for immediate classification of an SAE (e.g., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator will report the event by phone and by faxing a completed SAE form to the Sponsor (or designee) within 24 hours of knowledge of the event.	Text included in the updated protocol based on required section heading in new protocol template
Section 11.5.4, Overdose	Addition of text	The Investigator must immediately notify the Sponsor of any occurrence of overdose with study drug.	Text included in the updated protocol based on required section heading in new protocol template
Section 12, Statistical analysis	Addition of text	A Statistical Analysis Plan (SAP) will be prepared after the protocol is approved. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.	Text included in the updated protocol based on required

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		The SAP will serve as a compliment to the protocol and supersedes it in case of differences. The statistical evaluation will be performed using the Statistical Analysis Software (SAS®) Version 8.1 or higher (SAS Institute, Cary, NC). All data will be listed, and summary tables will be provided. Summary statistics will be presented by dose group. For continuous variables, data will be summarized with the number of participants (N), mean, standard deviation, median, minimum, and maximum by treatment group. For categorical variables, data will be tabulated with the number and proportion of participants for each category by treatment group.	section heading in new protocol template
Section 12.5, Interim Analysis	Created section	Section 12.5: Interim Analysis	Section heading was created based on information available in previous protocol under "Design" section
Section 12.6, Data Monitoring Committee	Addition of text	An independent Data Monitoring Committee (DMC) will be established by the Sponsor to review accumulating safety data at regular intervals throughout the study and monitor overall study conduct. The DMC will also evaluate results of a formal interim efficacy analysis. The DMC can recommend in writing to the Sponsor whether to continue, modify, or stop the clinical study on the basis of efficacy and safety considerations. The DMC's specific duties as well as statistical monitoring guidelines and procedures will be fully described in a DMC Charter.	Text included in the updated protocol based on required section heading in new protocol template
Section 13.1.1, Regulatory Guidelines	Addition of text	This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the Code of Federal Regulations (CFR), and in compliance with good clinical practice (GCP) guidelines.	Text included in the updated protocol based on required section heading in new protocol template
Section 13.1.2, Institutional Review Board/Independent Ethics Committee	Addition of text	Conduct of the study must be approved by an appropriately constituted Independent Ethics Committee (IEC)/IRB. Approval is required for the study protocol, investigational drug brochure, protocol amendments, informed consent forms (ICFs), and participant information sheets.	Text included in the updated protocol based on required section heading in new protocol template

Document	Change	Changes To The Protocol	Rationale for Change
Section 13.1.3, Informed Consent	Change of text	Section heading "Informed Consent Procedures" was changed to "Informed Consent"	To match with the current template heading
Section 13.3, Data Handling	Addition of text	Any data to be recorded directly on the eCRFs (to be considered as source data) will be identified at the start of the study. Data reported on the eCRF that are derived from source documents should be consistent with the source documents, or the discrepancies must be explained. Clinical data will be entered on eCRFs for transmission to the Sponsor. Data on eCRFs transmitted via the web-based data system must correspond to and be supported by source documentation maintained at the study site, unless the study site makes direct data entry to the databases for which no other original or source documentation is maintained. In such cases, the study site should document which eCRFs are subject to direct data entry and should have in place procedures to obtain and retain copies of the information submitted by direct data entry. All study forms and records transmitted to the Sponsor must carry only coded identifiers such that personally identifying information is not transmitted. The primary method of data transmittal is via the secure, internet-based electronic data capture (EDC) system maintained by inVentiv Health Clinical. Access to the EDC system is available to authorized users via the study's Internet web site, where an assigned username and password are required for access. Any changes made to data after collection will be made through the use of Data Clarification Forms. eCRFs will be considered complete when all missing and/or incorrect data have been resolved.	Text included in the updated protocol based on required section heading in new protocol template
Section 13.4, Source Documents	Addition of text	Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data or other activities in a clinical study necessary for the reconstruction and evaluation of the study.	Text included in the updated protocol based on required section heading in new protocol template

Document	Change	Changes To The Protocol	Rationale for Change
Section 13.5, Record Retention	Addition of text	Study records and source documents must be preserved for at least 15 years after the completion or discontinuation of/withdrawal from the study or 2 years after the last approval of a marketing application in an International Conference on Harmonization region, whichever is the longer time period. The Investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of participant health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR, Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 [HIPAA] Privacy Regulation). The Investigator shall ensure that study participants authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the Sponsor.	Text included in the updated protocol based on required section heading in new protocol template
Section 13.8.1, Protocol Amendment	Addition of text	Amendments to the protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no impact on the safety of participants or the conduct of the study will be classed as administrative amendments and will be submitted to the IRB/IEC for information only. The Sponsor will ensure that acknowledgement is received and filed. Amendments that are classed as substantial amendments must be submitted to the appropriate Regulatory Authorities and the IRBs/IECs for approval.	Text included in the updated protocol based on required section heading in new protocol template
Section 13.8.2, Protocol Deviations	Addition of text	Should a protocol deviation occur, the Sponsor must be informed as soon as possible. Protocol deviations and/or violations and the reasons they occurred will be included in the clinical study report. Reporting of protocol deviations to the IRB/IEC and in accordance with applicable Regulatory Authority mandates is an Investigator responsibility.	Text included in the updated protocol based on required section heading in new protocol template
Section 13.9, Ethical Considerations	Addition of text	This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the CFR, and in compliance with GCP guidelines. IRBs/IECs will review and approve this protocol and the ICF. All participants are required to give written informed consent prior to participation in the study.	Text included in the updated protocol based on required section heading in new protocol template
Section 13.10, Financing and Insurance	Addition of text	Prior to the study commencing, the Sponsor (or its designee) and the Investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial	Text included in the updated protocol based on required

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		agreement that will be signed by the Investigator (or the institution signatory) and the Sponsor (or its designee). The Investigator is required to have adequate current insurance to cover claims for its negligence and/or malpractice. The Sponsor, or the manufacturer of the study drug, will provide insurance coverage for the clinical study as required by national regulations.	section heading in new protocol template
Section 13.11, Publication Policy / Disclosure of Data	Addition of text	Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the Investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the Institution and the Sponsor or their designee.	Text included in the updated protocol based on required section heading in new protocol template
Final Protocol 05 Dec 2016 ((Location in Protocol Version 28 Sept 2016)			
Synopsis	Change of text	Number of Investigator/Study sites increased to more than 1 site	
Main Inclusion Criteria	Change of text	#3 Changed text from "by MSKCC" to "the enrolling site" #5 Changed text from who have "PD" to "primary progressive disease" #9e,f from "MSKCC" to "institution's" upper limit of normal #9g changed from Serum creatinine > 1.5x to Serum creatinine < 1.5x	
Main Exclusion Criteria	Change of text	#1 Text changed from "Consult the study MSKCC Principal Investigator" to "Consult the study Medical Monitor"	
Section 5.2.3, Exploratory Endpoints and Section 12.3.3, Analysis of Exploratory Efficacy Endpoints	Change of text	Changed text to will be analyzed at "a Parker Institute for Cancer Immunotherapy selected testing center" from "Memorial Sloan Kettering Cancer Center"	
Section 7, Selection and Withdrawal of Participants	Change of text, added text	Changed text from "on the clinicaltrials.gov website and on the Memorial Sloan Kettering Cancer Center website" to "the institution's website" Added the following text: "Participants must meet the inclusion and exclusion criteria; no exceptions will be made for enrollment"	

Document	Change	Changes To The Protocol	Rationale for Change
Section 9.2.1.1/9.2.2	Change of text	Changed text from "by a MSKCC pathologist" and per "MSKCC guidelines" to "the institution's" pathologist and "the institution's" guidelines	
Section 10.1.2, Target Lesions	Added section	Section 10.1.2.3, Lymph Nodes	To be consistent with RECIST v1.1
Section 10.1.5, Best Response	Deleted and added text	Deleted "Unequivocal progression of existing non-target lesions, other than pleural effusions without cytological proof of neoplastic origin, in the opinion of the treating physician within 8 weeks of study entry is also considered increasing disease (in this circumstance an explanation must be provided)." Added "In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm."	To be consistent with RECIST v1.1
Section 11.1.2, Serious Adverse Events	Deleted, added text	Deleted text referring to Clinical Research Database (CRD) and added text indicating inVentiv Health Clinical will manage SAEs using ARGUS. Also added text "Disease Progression is considered a non-reportable event".	Other sites do not have access to MSKCC CRD
Section 11.1.4, Overdose	Added text	Added "Overdose is defined as any dose higher than the dose specified to be administered in accordance with the protocol. All overdoses should be reported to inVentiv as SAEs (see Section 11.1.2). Details of signs and symptoms, clinical management, and outcome should be reported, if available. Overdoses should also be captured as protocol deviations."	
Section 11.2, Unexpected Problems/Non-Compliance	Created section	Section 11.2: Unexpected Problems/Non-Compliance	Section created to include text on unexpected problems, non-compliance issues
Section 12.6, Data Monitoring Committee	Deleted section, added text	Data Monitoring Committee (DMC) section deleted. Replaced with Data Monitoring section	Now using Data Review Team (DRT); see Section 12.6.1
Section 12.6.1, Date Review Team	Added text	Added text describing Data Review Team	
Section 13.2, Research Participant Registration	Change of text	Interactive Voice Response vendor changed to Almac	
Section 13.6, Monitoring	Deleted text, added text	Deleted old text and added new text describing monitoring procedures	
Section 13.8.2, Protocol Deviations	Deleted text	Deleted "as soon as possible" from the sentence "Should a protocol deviation occur, the Sponsor must be informed as soon as possible".	
Section 15.3, Tumor tissue specimens	Change of text	Text updated to include 3 core biopsies snap frozen and 1 biopsy formalin fixed and preserved in paraffin embedded blocks	

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Section 15.3, RNA and DNA Preparation/Exploratory Serum and Plasma Biomarkers	Change of text	Changed text from "PAXgene tube" to "lavender top tube"	
Table 3: Schedule of Assessments	Deleted text	"Additional Follow-Up Visits" column updated to include only AEs and Survival Data	
Appendix 3	Addition of text	Added text describing shipping and testing of samples	
Final Protocol 23 Jan 2017			
Title Page, Synopsis, Document Header	Change of text	Protocol number changed from 16-043 A to PICI0001	To clarify transition from Investigator Initiated Trial to Sponsor Trial
Investigator Protocol Agreement Page	Deleted text	Deleted investigator name "Jedd Wolchok"	Cell should be blank to allow each investigator to print their name
Section 3, List of Abbreviations	Deleted text / Addition of text	Deleted "RSA / Research Study Assistant" and added "SC / Study Coordinator." Added "IVR / Interactive Voice Recognition."	
Section 6.1.2, Randomization	Change of text	Added text indicating that an IVR system will be used to manage randomization	
Section 11.2, Unanticipated Events / Non-Compliance	Change of text	In section title, first subsection title, and first subsection text, changed instances of "Events" or "event" to "Problems" or "problem." This section was revised to clarify the investigator's responsibility for reporting.	
Section 13.3, Data Handling	Change of text	Changed "Research Study Assistant / RSA" to "Study Coordinator / SC."	
Section 13.8.1, Protocol Amendment	Change of text	This section was revised to indicate that any change to the protocol, whether substantial or minor, will require a formal amendment.	
Section 13.8.2, Protocol Deviations	Change of text	This section was revised to clarify the investigator's responsibility to report protocol deviations and where they are to be reported, and to indicate that prospective deviation requests will not be allowed.	
Final Protocol 06 Mar 2018 (Location in Protocol Version 05 Dec 2016)			
Synopsis	Changed text	Revised the synopsis to be consistent with changes to the body of the protocol (described below).	

Document	Change	Changes To The Protocol	Rationale for Change
Section 6.1, Description of Overall Study Design and Plan, Section 6.2, Discussion of Study Design, and Section 12.1, Determination of Sample Size	Changed text	Revised the text to reflect the change in total sample size from 70 participants (35 per arm) to 24 participants (12 per arm).	Sponsor decision to lower overall accrual goal due to challenges with enrollment, competing trials, and available participant population.
Section 7.1, Inclusion Criteria	Changed text	Criterion #4: Removed language that defined "primary progression participants" and "participants with relapsed disease". Added language to indicate that any participant who had refractory or relapsed disease is eligible for study enrollment.	Broadening of eligibility criteria to make clinical trials more representative.
Section 7.2, Exclusion Criteria	Changed text	Criterion #1: Clarified the eligibility of participants with concurrent malignancies.	Broadening of eligibility criteria to make clinical trials more representative.
Section 8.3, Treatment of Nivolumab or Ipilimumab Related Infusion Reactions	Removed text	Removed the use of "mild", "moderate", and "severe" language.	Clarity
Section 8.4.1, Dosage and Administration and Section 15.1, Appendix 1, Product Information and Pharmacy Manual	Added text	Added text to indicate that infusion times are approximate.	Clarity
Section 8.4.2, Monitoring and Dose Delay Criteria	Added text	Added text to indicate that participants should follow timed assessments and that continuation on study is at the principal investigator's discretion.	Clarity
Section 9, Study Procedures (Table 3 – Schedule of Assessments)	Added text	Added a separate column for "Early Termination Visit" to clearly define the end of treatment visit and the assessments that need to be collected as part of the Early Termination Visit.	Clarity
	Added text	Added a footnote to clarify survival for participants who progress (ie, after disease progression participants are not required to have scans every 12 weeks but instead, survival could be assessed via calls every 3 months ± 7 days).	Clarity
	Added text	Added a footnote to clarify CT scan assessment intervals and the minimum scan requirements.	Clarity
Section 11.1.2, Serious Adverse Event	Changed text	Revised text to clarify that hospital admission for elective pre-planned surgeries is not considered an SAE.	Clarity

Document	Change	Changes To The Protocol	Rationale for Change
SAE Reporting to BMS and inVentiv	Added text	Added text to indicate that all AEs are to be followed until resolution, until a stable clinical endpoint is reached, or for 100 days after the last dose of study treatment, unless other anticancer therapy is initiated.	Clarity
Section 11.1.3, Pregnancy	Added text	Revised text to clarify pregnancy-related information.	Clarity
Section 11.1.5, Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events	Added new section	Added this section to specify that progression of cancer under study, as judged by the Investigator, is not considered a reportable adverse event.	Clarity
Section 12.4, Safety Analysis	Changed text	Removed reference to interim analysis.	Section removed as interim analysis is no longer required.
Section 13.11, Study and Site Closure	Added new section	Added this section to specify the procedure for study and site closure.	
Section 15.1, Appendix 1, Product Information and Pharmacy Manuals	Changed text	Updated the text regarding dose calculations based on body weight to indicate that dose adjustments are only required for participants who have a 10% change compared with their initial weight on Cycle 1, Day 1.	Clarity
Section 15.3, Appendix 3, Laboratory Procedures	Changed text	Gene expression profiling: Removed reference to the specific method and instead indicate that gene expression profiling will be run using different methodologies. RNA and DNA preparation: Revised text to indicate that DNA or RNA will be extracted from any core biopsy (not just fresh snap frozen core biopsies). Exploratory serum and plasma biomarkers: Removed the language that required 4 CPT tubes and 1 lavender top tube to be collected.	Clarity
Section 15.4, Appendix 4, Contraceptive Guidance and Collection of Pregnancy Information	Added new appendix	Added this appendix to provide pregnancy-related information and specific guidance for contraception.	

SPONSOR APPROVAL PAGE

Date: 3/6/18

Ramy Ibrahim, M.D.
Vice President, Clinical Development

INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by Parker Institute for Cancer Immunotherapy.
- Not to implement any changes to the protocol without written agreement from Parker Institute for Cancer Immunotherapy and prior review and written approval from the Independent Ethics Committee (IEC) except where necessary to eliminate an immediate hazard to participants.
- That I am thoroughly familiar with the appropriate use of the study drug, as described in this protocol and any other information provided by Parker Institute for Cancer Immunotherapy including, but not limited to, the current Investigator's Brochure (IB).
- That I am aware of, and will comply with, good clinical practices (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the Parker Institute for Cancer Immunotherapy study drug and of their study-related duties and functions as described in the protocol.

Signature: _____ Date: _____

Name (print): _____
Principal Investigator

Site Number: _____

1 SYNOPSIS

Title of Study:	A Randomized, Phase 2 Study of Ipilimumab vs Ipilimumab plus Nivolumab in Participants with Stage III-IV Melanoma Who Have Progressed or Relapsed on PD-1 Inhibitor Therapy
Protocol Number:	PICI0001
Investigators/Study Sites:	This study will be conducted at multiple sites in the United States.
Phase of Development:	2
Objectives:	**Primary Objectives:** To assess response rates of combination ipilimumab/nivolumab and ipilimumab alone in participants previously treated with a programmed death receptor (PD-1) inhibitor by Week 18 of therapy. **Secondary Objectives:** • To assess clinical benefit of combination ipilimumab/nivolumab and ipilimumab alone • To evaluate time to treatment failure and overall survival (OS) for each arm • To assess safety and tolerability of ipilimumab alone and in combination with nivolumab in previously treated participants **Exploratory Objectives:** • To evaluate peripheral lymphocyte phenotype changes throughout treatment • To evaluate changes in quantities of myeloid derived suppressor cells (MDSCs), defined as CD14+HLA-DR^{low} cells, and T_{reg} cells, defined as CD4+FOX3P+ cells, throughout treatment • To evaluate nCounter immune profiling of the tumor before treatment • To explore tumor neoepitopes and mutational burden via whole gene and exome sequencing on pre-treatment tumor biopsy and correlation with clinical response • To stratify clinical response rate by PD-L1 expression on pre-treatment biopsies • To evaluate the tumor immune microenvironment on pre- and on-treatment tumor biopsies
Study Design:	This is a multi-center, randomized Phase 2 study of ipilimumab vs ipilimumab plus nivolumab in participants previously treated with a PD-1 inhibitor by Week 18 of therapy. There will be 2 arms in the study. **Arm A**: Participants will receive combination checkpoint blockade with ipilimumab and nivolumab. **Arm B**: Participants in this arm will receive ipilimumab alone. A Simon 2-stage design will be implemented in each arm, allowing for early stopping for futility. Participants who are eligible will be required to have a pre-treatment biopsy and then will be randomized to either ipilimumab alone or ipilimumab in combination with nivolumab. Participants will be required to have an on-treatment biopsy within 14±5 days of their first dose of treatment. Participants will receive up to 4 cycles of treatment followed by observation phase. Participants will be assessed for the primary endpoint at 18 weeks and then be followed for time to treatment failure (TTF) and OS for up to 2 years.

Selection of Participants:	Main Inclusion Criteria: 1. AJCC (2009) Stage IV cutaneous melanoma or Stage III cutaneous, acral or mucosal melanoma that is judged inoperable. Participants with a history of uveal melanoma are not eligible. 2. Measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm with conventional techniques or as >10 mm with computerized tomography (CT) scan. Participants must have at least one measurable lesion by Response Evaluation Criteria in Solid Tumors (RECIST) and a separate lesion amenable to biopsy. 3. Histologic proof of melanoma reviewed and confirmed by the enrolling site. 4. Previous treatment with a PD-1 or PD-L1 inhibitor with documented progression of disease on most recent CT scan. Progression of disease is defined as 1) the appearance of a new measurable lesion (>10 mm) on cross-sectional imaging or physical examination OR 2) enlargement of previously detected lesions on two consecutive imaging studies OR 3) enlargement of a previously detected lesion with correlative symptomatology on one cross-sectional imaging study. Participants remain eligible if they had a previous response to a PD-1 inhibitor, including participants who had a complete response, partial response or stable disease (SD). Any participant who had refractory or relapsed disease is eligible for study enrollment. Treatment populations are defined in Section 12. 5. Participants who received adjuvant PD-1 therapy who then develop measurable disease are eligible. However, they must have received their last dose of PD-1/PD-L1 blockade within two months of enrollment in this study. They will be stratified with participants who have primary progressive disease. 6. Life expectancy of greater than 3 months. 7. Age ≥ 18 years old. 8. Eastern Cooperative Oncology Group performance status = 0 or 1 or Karnofsky Performance Status equivalent. 9. Participants must have adequate organ and marrow function as defined below: a. White blood cells >2, 000/mcL b. Absolute neutrophil count >1,500/mcL c. Platelets >100,000/mcL d. Hemoglobin > 9.0 g/dL e. Total bilirubin ≤ 1.5 X institution's upper limit of normal f. Aspartate aminotransferase (serum glutamic oxaloacetic transaminase)/alanine aminotransferase (serum glutamic pyruvic transaminase) ≤ 2.5 X institution's upper limit of normal for participants with no concurrent liver metastases, OR ≤ 5 X institution's upper limit of normal for participants with concurrent liver metastases g. Serum creatinine < 1.5x OR creatinine clearance of at least 40 10. Women of childbearing potential must have a negative serum pregnancy test within 24 hours prior to the start of study drug. A woman of childbearing potential is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over age 50 in the absence of other biologic or physiologic causes.

	11. Women with child bearing potential and men with reproductive potential must be willing to practice acceptable methods of contraception. 12. Ability to understand and the willingness to sign a written informed consent document. 13. Willingness to undergo biopsy of metastatic site or site of unresectable disease prior to randomization. Main Exclusion Criteria: 1. Concurrent malignancies: a. Participants with a previously treated malignancy are eligible to participate if all treatment of that malignancy was completed at least 2 years before registration and the participant has no evidence of disease. b. Participants who have a concurrent malignancy that is clinically stable and does not require tumor-directed treatment are eligible to participate if the risk of the prior malignancy interfering with either safety or efficacy endpoints is very low (with agreement from the sponsor and principal investigator). c. Other malignancies may be permitted if the risk of the prior malignancy interfering with either safety or efficacy endpoints is very low (with agreement from the sponsor and principal investigator). 2. Any major surgical procedures or external beam radiotherapy within 14 days prior to study drug administration. 3. Use of other investigational drugs within 28 days prior to study drug administration. 4. Symptomatic or untreated leptomeningeal or brain metastases or spinal cord compression. Treated brain metastases must have been stable for at least 1 month and require treatment with less than 10mg/day prednisone equivalent for at least 2 weeks prior to study drug administration. 5. Prior exposure to either ipilimumab or combined checkpoint blockade. 6. Any diagnosis of autoimmune disease. Participants with Type I diabetes mellitus, hypothyroidism only requiring hormone replacement, adrenal insufficiency on replacement dose steroids, skin disorders (such as vitiligo, psoriasis or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll. 7. Pregnant women and lactating women. 8. History of uveal melanoma. 9. Known Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection (with the exception of chronic or cleared HBV or HCV infection, which will be allowed). Once-documented negative result for HIV, HBV, and HCV is sufficient. 10. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection and psychiatric illness/social situations that would limit compliance with study requirements. 11. Participants with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement steroid doses > 10 mg daily prednisone equivalent are permitted.

	12. Participants with history of any grade 4 toxicity during previous anti PD-1 treatment or history of Grade 3 or higher pneumonitis. 13. Participants with a history of Grade ≥2 neuropathy. 14. Prisoners or participants who are involuntarily incarcerated. 15. Children under the age of 18. 16. Participants who require hemodialysis. 17. Participants with a history of allergy to study drug components or history of a severe hypersensitivity reaction to any monoclonal antibody.
Planned Sample Size:	Twelve participants will be enrolled in each arm for a total of 24 participants.
Investigational Therapy:	Not Applicable
Reference Therapy:	Arm A: Nivolumab (1 mg/kg of body weight) in combination with ipilimumab (3 mg/kg), both once every 3 weeks for 4 doses administrated intravenously. Or Arm B: ipilimumab (3 mg/kg) alone, once every 3 weeks for 4 doses administrated intravenously.
Treatment Duration:	Participants on both arms will receive treatment for up to 4 cycles (each cycle is of 21 days±4 days) and then be observed for up to 2 years in the follow up period. Participants will undergo screening and, if eligible, will undergo intervention in the selected arm of the study up to 4 cycles.
Criteria for Evaluation:	Efficacy: Therapeutic response and outcome assessment will be done in this study using the international criteria proposed by the RECIST version 1.1 Committee. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Lesions are either measurable or non-measurable. "Target" and "Non-Target" lesions will be identified and recorded at baseline. Responses will be assessed as follows: • Complete Response (CR): Disappearance of all target and non-target lesions and no evidence of new lesions documented by 2 disease assessments at least 4 weeks apart. • Partial Response (PR): At least a 30% decrease in the in the longest dimension (LD) of all target lesions, taking as reference the baseline sum LD. There can be no unequivocal progression of non-target lesions and no new lesions. Documentation by 2 disease assessments at least 4 weeks apart is required. Progressive Disease (PD): At least a 20% increase in the sum of LD of target lesions, taking as reference the smallest sum LD or the appearance of new lesions within 8 weeks of study entry. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. • Stable Disease (SD): Any condition not meeting the above criteria. • Inevaluable for response is defined as having no repeat tumor assessments following initiation of study therapy for reasons unrelated to symptoms or signs of disease. Outcome will be assessed as follows: • Objective Response Rate (ORR): The proportion of participants with either (1) CR or (2) PR by RECIST 1.1 criteria. • Survival: The observed length of life from first dose of study drug to death or the date of last contact. • Time to treatment failure: Is defined as the time from first study drug treatment until the participant is started on another line of systemic therapy or participant death, whichever occurs first. Participants who

	are alive and do not start another therapy will be censored at the time of last follow-up. Safety: Safety assessments (vital signs, physical examinations, performance status, height/weight, electrocardiogram (ECG) recording, adverse events (AEs), clinical laboratory results (routine hematology and biochemistry, and CT and magnetic resonance imaging [MRI] scans) are to be performed at protocol-specified visits.
Study Endpoints:	Primary endpoints: • The response to combination ipilimumab/nivolumab and ipilimumab alone at Week 18 defined as having achieved a complete response or PR as measured by RECIST 1.1 criteria or a PR/complete response at any time prior to Week 18. Secondary endpoints: • Disease control rate (DCR) by RECIST v1.1 criteria of overall tumor burden at Week 12 and Week 18. DCR is defined as participants who achieve SD, PR or complete response. • TTF and OS up to 2 years. • Safety and tolerability measured via metrics such as laboratory tests, vital signs, physical examinations as well as toxicity as graded by Common Terminology Criteria for Adverse Events v4.0. Exploratory endpoints: • All research samples for exploratory endpoints will be analyzed at a Parker Institute for Cancer Immunotherapy selected testing center. • Peripheral lymphocyte phenotype changes throughout treatment, including T_{reg} cells, defined as CD4+FOX3P+ cells, will be expressed using descriptive statistics at pre and post treatment time points. These will be assessed via flow cytometry of peripheral blood mononuclear cells. • Changes in quantities of MDSCs, defined as CD14+HLA-DR^{low} cells, throughout treatment will be expressed using descriptive statistics at pre and post treatment time points. • nCounter immune profiling of the tumor before treatment will be expressed using descriptive statistics at pre and post treatment time points and will be correlated with clinical response also using logistic regression models. • Tumor neoepitopes and mutational burden will be correlated with clinical response also using logistic regression models. • Summary statistics will be generated and differences between mutation burden or neo-antigen score as they relate to PD-L1 expression • Immunohistochemistry (IHC) will be used to assess PD-L1 expression on both immune cells and tumor cells. PDL-1 expression will be assessed pretreatment and on-treatment. A participant will be PD-L1 + if >1% of cells express PD-L1. If response data permit, the tumor positivity of PD-L1 expression will be compared in the pre- and post-treatment biopsies using a Wilcoxon signed rank test. • Pre- and on- treatment PD-L1 expression and will be correlated with clinical response also using logistic regression models. • IHC will be used to quantify cytotoxic and regulatory T-cells, including stains for CD3, CD4, CD8, FOXP3, inducible co-stimulatory and Lag3. Associations from pre to post treatment will be assessed using the Wilcoxon signed rank test for paired

	comparisons (e.g., the continuous measure, density of cells per high powered field).
Statistical Methods and Planned Analyses:	This is a multi-center, randomized, Phase 2 study of ipilimumab and combined checkpoint blockade with ipilimumab and nivolumab. Randomization will be performed via a central process. In each arm, an optimal Simon 2-stage design will be implemented. A response rate of 10% or less would not be considered promising (null hypothesis) as the ipilimumab response rate in untreated participants is 10.9%. A response rate of at least 30% is promising (alternative hypothesis). Point estimates and 95% confidence intervals for the response rates will be reported. Alpha (probability of Type I error) for hypothesis tests will be 0.1. If 4 or more of 12 participants in an arm respond (response rate of 33% or greater), the treatment will be considered promising for further investigation. **Efficacy evaluable population:** All participants who receive at least 1 dose of study drug(s) will be evaluated for the primary endpoint. Participants who develop rapid symptomatic disease progression or drop out early due to death will be treated as non-responders. Participants who develop early toxicities that require treatment delay or discontinuation will continue to be evaluable on study. Participants may be replaced in either arm if they complete randomization but do not complete any cycles of therapy. **The toxicity evaluable population**: Participants who have completed at least 1 treatment cycle on either arm will be considered evaluable for toxicity. **Preferable treatment arm will be decided as follows**: • If both arms have comparable response rates, the investigators will perform a comprehensive review of both the response data and toxicity data to decide which study arm is the preferable treatment moving forward.

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IN-TEXT TABLES

IN-TEXT FIGURES

3 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration versus time curve
BMS	Bristol-Myers Squibb
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence Interval
CL	Clearance
C_{max}	Peak concentration
C_{min}	Trough concentration
CMP	Comprehensive metabolic panel
CR	Complete Response
CRO	Contract Research Organization
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DILI	Drug induced liver injury
DRT	Data Review Team
DSM	Data and Safety Monitoring
DTIC	Dacarbazine
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EORTC	European Organisation for Research and Treatment of Cancer
FDA	Food and Drug Administration
FFPE	Paraffin embedded blocks
GCP	Good Clinical Practice
gp100	Glycoprotein 100
HBV	Hepatitis B Virus
HCG	Human chorionic gonadotropin
HCV	Hepatitis C Virus

HIPAA	Health Insurance Portability Accountability Act
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICOS	Inducible co-stimulatory
IDE	Investigational Device Exemption
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
IVR	Interactive Voice Recognition
LD	Longest dimension
LDH	Lactate dehydrogenase
MDSCs	Myeloid derived suppressor cells
MRI	Magnetic resonance imaging
MSKCC	Memorial Sloan-Kettering Cancer Center
NCI	National Cancer Institute
OR	Objective response
ORR	Objective Response Rate
OS	Overall survival
PBMCs	Peripheral blood mononuclear cells
PD	Progressive Disease
PD-1	Programmed death receptor
PFS	Progression-free survival
PI	Principal Investigator
PPR	Protocol Participant Registration
PR	Partial Response
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SC	Study Coordinator
SD	Stable Disease
SEER	Surveillance, Epidemiology, and End Results
TEAE	Treatment-emergent adverse events
T_{regs}	Regulatory T-cells
TSH	Thyroid-stimulating hormone
TTF	Time to treatment failure
ULN	Upper limit of normal
WBC	White blood cell

4 INTRODUCTION

4.1 Background on Melanoma

Epidemiology and Prognosis of Cutaneous Melanoma

According to the Surveillance, Epidemiology, and End Results (SEER) database, there was an estimated 73,870 new cases of melanoma diagnosed in the United States in 2015. There will be an estimated 9,940 deaths due to metastatic disease. The incidence of melanoma continues to increase dramatically, at an overall rate of 33% for men and 23% for women from 2002 to 2006.1 Approximately 9% of patients present with regional metastases (Stage III disease) and 4% present with distant disease; however, patients with Stage III disease who have full surgical resection remain at an elevated risk of disease recurrence and death. Data from our Center show that the 5-year relapse-free survival for Stage IIIC melanoma is 15%.2 Data from the SEER database demonstrates a 5-year overall survival (OS) rate of 16.6%.

Chemotherapy in the treatment of metastatic melanoma

Prior to the advent of immunotherapy, chemotherapy was the mainstay of treatment of metastatic melanoma. Dacarbazine (DTIC) is the only single-agent chemotherapy approved by the Food and Drug Administration (FDA) for treating patients with metastatic melanoma, with an approximate 20% objective response rate, a median response duration of 5 to 6 months and complete response rates of 5%.3 Numerous agents were tried alone and in combination to treat metastatic melanoma as summarized in the chart below. However, response rates were modest, ranging from 13.5% to 26%, and OS remained dismal, with median survival for the most part measured in months and the majority of patients surviving less than one year. The lack of efficacy of traditional chemotherapy prompted research efforts to find alternative treatments.

Table 1: Published Trials of Chemotherapy in Metastatic Melanoma

Investigator	Study Treatment	Response Rate	Overall Survival	Progression-Free Survival
Wiernik et all,19934	Paclitaxel	16.4%	NR	NR
Bajetta et al, 19945	DTIC	20%	11 months	NR
Middleton et al, 20006	DTIC, BCNU, Cisplatin and tamoxifen	26.4%	202 days	NR
Chapman et al, 19997	DTIC, BCNU, Cisplatin and tamoxifen	18.5%	7 months	NR
Middleton et al, 20008	Temozolomide	13.5%	7.7 months	1.9 months
Rao et al, 20069	Carboplatin/paclitaxel	26%	7.8 months	3 months
Hersh et al, 2010[10]	Albumin-bound Paclitaxel	2.7% in previously treated patients; 21.6% in chemo naïve patients	12.1 months; 9.6 months	3.5 months; 4.5 months
Flaherty et al, 2013[11]	Carboplatin/paclitaxel/ Sorafenib	20%	11.3 months	4.9 months

Early immunotherapy

High dose interferon was the initial immunotherapy used in the adjuvant setting for patients with either Stage IIB or Stage III disease. In the Eastern Cooperative Oncology Group (ECOG) 1684 trial, 287 patients were randomly assigned to one year of high dose IFNa-2b or observation. Treatment with high dose interferon resulted in a nine-month prolongation in relapse-free survival (RFS, median 1.7 versus 1.0 years) with an 11% absolute increase in RFS at five years (37% vs 26%).[12] However, there was no difference in OS on later analysis.[13] The RFS benefit of high dose interferon was confirmed in the intergroup E1690 trial which compared high dose IFNa to low dose IFNa vs observation, but again, no OS benefit was seen.[14] In the EORTC 18991 trial, patients with Stage III melanoma were randomized to pegylated IFNa or observation. The 7 year RFS was increased with IFNa compared with observation (39.1% vs 34.6%) but again there was no difference in OS.[15] Interestingly, a recent meta-analysis of all patients treated with adjuvant IFNa did demonstrate an OS benefit.[16]

In patients with metastatic disease, high dose IL2 demonstrated a clinical benefit. In 270 patients treated between 1985 and 1993, the objective response rate was 16%, including 17 complete responses (CRs).[17] Median duration of the CRs was greater than 59 months.[18] However, 6 patients (2%) died from adverse events (AEs), all related to sepsis.

The tumor immune microenvironment

There are a number of changes in the tumor immune microenvironment that are induced by both CTLA-4 and programmed death receptor (PD-1) blockade to inhibit adaptive immune resistance. A clinical response to ipilimumab has been found to be associated with increased infiltration of tumor infiltrating lymphocytes [19] and of CD4 T cells expressing the inducible co-stimulatory (ICOS) molecule.[19] CD8+ T cell expression at the invasive tumor margin has found to be predictive of response to PD-1 blockade[21], as has a more clonal T-cell receptor repertoire.[21] Interestingly, both classes of drugs are thought to decrease regulatory T-cells (T_{regs}) in the tumor microenvironment[22,23] which may dampen a cytotoxic T cell response.

Biomarkers for clinical response

Expression of PD-L1 has been found to be an unreliable biomarker.[24] The first Phase 1 trial with nivolumab demonstrated that only tumors that were PD-L1+ demonstrated an objective response rate (ORR)[25]; however, in another early phase trial of nivolumab, both PD-L1+ and PD-L1- patients responded, although PD-L1+ patients had a higher ORR, progression-free survival (PFS) and OS.[26] In patients treated with MPDL3280A, a PD-L1 inhibitor, PD-L1 expression on infiltrating immune cells but not tumor cells, was found to correlate with response.[27]

Gene expression profiling

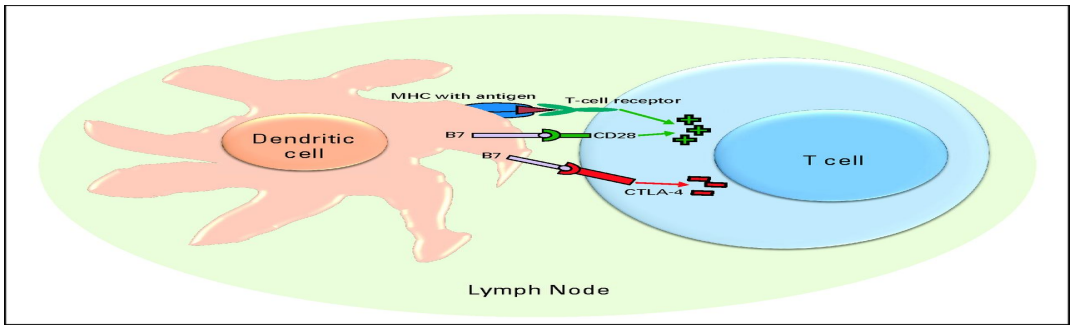
There is growing interest in examining gene expression related to the immune response which may correlate with response to checkpoint blockade or provide new insights into mechanisms of immune escape. Ribas and colleagues have found that two immune signatures analyzed using the NanoString nCounter were correlated with ORR and PFS.[28] Tumors expressing PD-L1 also appear to have upregulation of pathways involved in CD8+ T-cell activation, antigen presentation and immunosuppression.[29] Both studies underscore the importance of interferon-ɣ induced adaptive immune resistance as a mechanism of tumor escape.

4.2 Clinical Studies

Clinical development of CTLA-4 inhibitors

Normally after T-cell activation, CTLA-4 is upregulated on the plasma membrane where it functions to downregulate T-cell function through a variety of mechanisms, including preventing co-stimulation by outcompeting CD28 for its ligand, B7 and also by inducing T-cell cycle arrest.

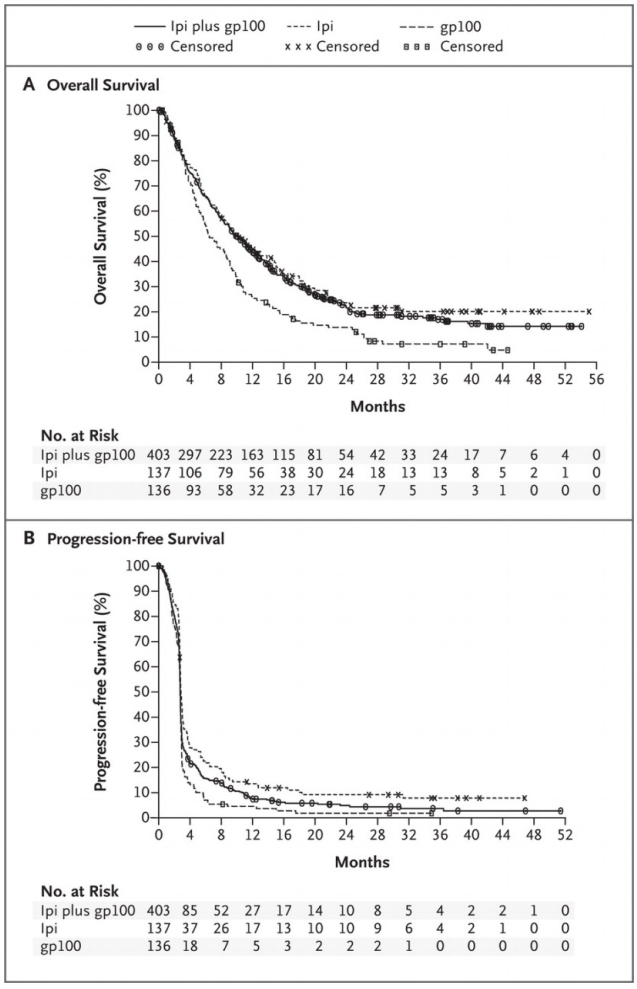
Figure 1: The Interaction between Antigen Presenting Cell and Cytotoxic T-cell via CTLA-4



Source: Postow et al, JCO 2015

On the basis of this preclinical rationale, an antibody targeting CTLA-4 now known as ipilimumab entered clinical development. Early reports showed durable clinical responses in some patients.[30-32] This was confirmed in two large Phase 2 trials. In the first trial, ipilimumab was administered with or without a glycoprotein 100 (gp100) peptide vaccine vs. gp100 alone in patients with previously treated metastatic melanoma. The median OS with ipilimumab alone was 10.1 months vs. 6.4 months among patients receiving gp100 alone (HR for death, 0.68; p<.001).[33] This represented a significant increase in median survival over chemotherapy alone, as discussed earlier.

Figure 2: Kaplan-Meier Curves for Overall Survival and Progression Free Survival Demonstrating a Survival Benefit in Patients Treated with Ipilimumab vs gp100 Vaccine Alone



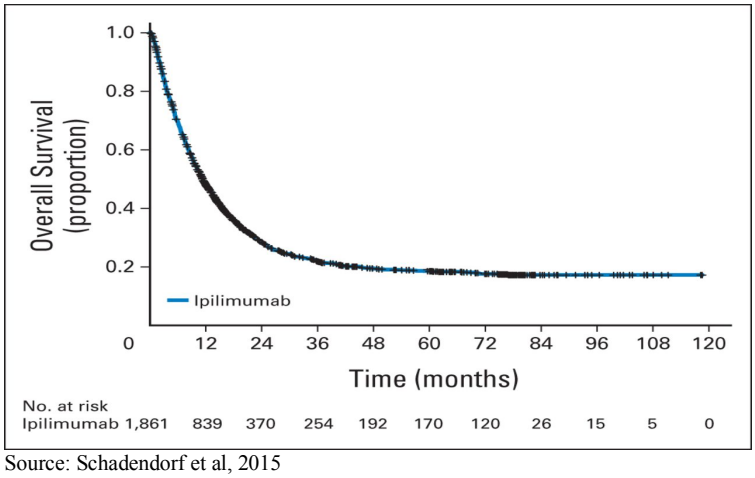
Source: Hodi et all, 2010

In the second trial, patients with previously untreated metastatic melanoma were assigned to receive ipilimumab plus dacarbazine vs dacarbazine plus placebo. Overall survival was significantly longer in the group receiving ipilimumab- dacarbazine vs dacarbazine plus placebo (11.2 months vs 9.1 months) with an associated OS advantage at three years (30.8% vs 12.2%).[34]

The long-term survival advantage of ipilimumab has been confirmed in a pooled analysis of 1,861 patients from 10 prospective and two retrospective studies. Patients were both previously treated (n=1,257) or treatment naïve (n=604). Overall median survival was 11.4 months (95% confidence interval (CI), 10.7 to 12.1 months), which included 254 patients with at least three years of survival. Three-year survival rates were 22%, 26%, and 20% for

all patients, treatment-naive patients, and previously treated patients, respectively.[35] This long-term survival rate demonstrated a marked improvement when compared to historical controls.

Figure 3: Primary Analysis of Pooled OS Data (3-year Survival Rate was 22%)



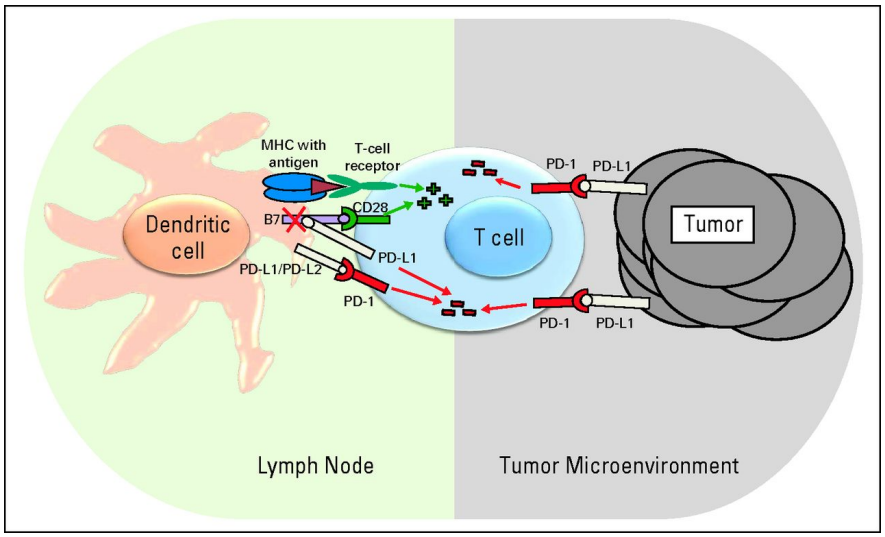
Source: Schadendorf et al, 2015

Patients who have had progressive disease (PD) after initial treatment with ipilimumab have also been able to be successfully retreated with ipilimumab.[36] The sum of this data led to its FDA approval for treatment of metastatic melanoma in March 2011.

Clinical development of PD-1 inhibitors

PD-1 is a negative regulator of T-cell activity that limits the activity of T cells at a variety of stages of the immune response when it interacts with its two ligands PD-L1 and PD-L2.[37] PD-1 is primarily believed to inhibit effector T-cell activity in the effector phase within tissues. This pathway is likely important in the tumor microenvironment where PD-L1 expressed by tumors interacts with PD-1 on T cells to suppress T-cell effector function by limiting T-cell receptor localization to the immunologic synapse at the site of target engagement.

Figure 4: The Role of PD-1 in Early T-Cell Activation

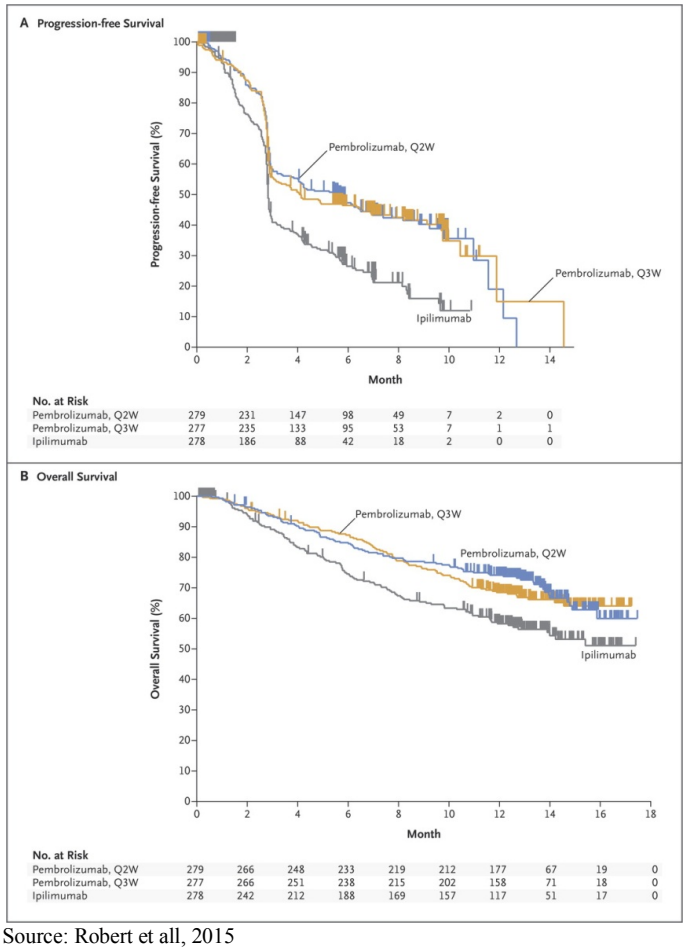


Source: Postow et al, JCO 2015

Anti-PD-1 antibodies have robust clinical activity, with a response rate of 17% in patients with metastatic melanoma in a Phase 1 multi-center study.[40] This was confirmed in several larger studies. In 107 patients with advanced melanoma who were treated with nivolumab, the ORR was 31% with a median OS of 16.8 months. Among patients who had an objective response, the median response duration was two years.[41] In another trial of patients who had previously received ipilimumab, patients who received pembrolizumab had a similar ORR of 26%.[42]

Most recently, 834 patients were enrolled in a randomized Phase 3 study of ipilimumab vs pembrolizumab, dosed either every 2 or 3 weeks. The ORR was 33.7% with pembrolizumab every 2 weeks, 33.9% every 3 weeks and 11.9% with ipilimumab (P<.001). The 12-month OS rates were 74.1%, 68.4%, and 58.2%, respectively.[43] The sum of these data lead to the FDA approval of both pembrolizumab and nivolumab for the treatment of metastatic melanoma.

Figure 5: Kaplan-Meier Curves for Overall Survival and Progression Free Survival Demonstrating a Survival Benefit in Patients Treated with Pembrolizumab Dosed Every Two or Three Weeks vs Ipilimumab



Source: Robert et all, 2015

Clinical development of combination checkpoint blockade

Strong preclinical rationale for the combined evaluation of combined CTLA-4 and PD-1 pathway blockade was provided by basic immunologic observations, which supported the notion that CTLA-4 and PD-1 are non-redundant pathways for regulation of T-cell responses. This hypothesis was first tested in a Phase 1 clinical trial of nivolumab plus ipilimumab in advanced melanoma. The ORR in the concurrent treatment group was 40%, but 53% in the patients who were treated with the maximum doses with an acceptable level of adverse effects.[44] This initial finding was confirmed in two Phase 3 trials in previously untreated patients.[45,46]

4.3 Rationale

Checkpoint inhibitors enhance antitumor immunity by blocking negative regulators of T-cell function that exist both on immune cells and on tumor cells. There are 2 classes of checkpoint

blockade currently FDA approved, CTLA-4 antibodies and PD-1 antibodies. CTLA-4 and PD-1 are non-redundant pathways for the regulation of T-cell responses; CTLA-4 is believed to regulate immune responses early in T-cell activation, while PD-1 is believed to inhibit T-cell effector function within the tissues. Interestingly, both agents are thought to decrease regulatory T cells in the tumor microenvironment, which may dampen a cytotoxic T cell response.

Ipilimumab blocks CTLA-4 and has a demonstrated survival benefit for patients with previously untreated advanced melanoma in two Phase 3 trials.[33,34] Nivolumab is a PD-1 antibody and has demonstrated a survival benefit both in patients with ipilimumab-refractory advanced melanoma [42,47] and in patients with previously untreated metastatic melanoma.41 The two agents have demonstrated a synergistic effect, consistent with their various pathways, in a large clinical trial of combination checkpoint blockade with an overall response rate 57.6%.[47]

PD-1 inhibitors are increasingly being utilized in the first-line treatment setting for metastatic melanoma due to a more favorable response rate and side effect profile compared to ipilimumab. However, as a result, there is no current standard of care for the 60% of patients who will have progressive or relapsed disease after single agent PD-1 blockade. While the response rate of PD-1 inhibitors in patients previously treated with ipilimumab is well known, there is no data for the efficacy of ipilimumab as a second agent. Moreover, combination checkpoint blockade has also never been tried in this population.

We hypothesize that by administering a CTLA-4 antibody to this population of PD-1 inhibitor pre-treated patients, we will activate alterative T-cell activation pathways and deplete regulatory T cells in the tumor microenvironment, thus increasing immune activation and resulting in clinical efficacy. We are interested in administering ipilimumab both as a single agent and in combination with nivolumab to explore whether dual checkpoint blockade synergy is as active in a pre-treated population as in a treatment-naïve population. In addition, given the elevated toxicity rates associated with combination checkpoint blockade, it is important to assess toxicity profiles in both single and combined immunotherapy approaches in this pre-treated population.

Thus, we propose this randomized, parallel single arm, 2-stage Phase 2 study to assess response rates to ipilimumab alone and in combination with nivolumab in participants who have progressed after anti-PD-1 therapy.

5 STUDY OBJECTIVES AND ENDPOINTS

5.1 Study Objectives

5.1.1 Primary Objective

The primary objective is to assess response rates of combination ipilimumab/nivolumab and ipilimumab alone in participants previously treated with a PD-1 inhibitor by Week 18 of therapy.

5.1.2 Secondary Objectives

The Secondary Objectives are:

- To assess clinical benefit of combination ipilimumab/nivolumab and ipilimumab alone

- To evaluate time to treatment failure and OS for each arm
- To assess safety and tolerability of ipilimumab alone and in combination with nivolumab in previously treated participants.

5.1.3 Exploratory Objectives

- To evaluate peripheral lymphocyte phenotype changes throughout treatment
- To evaluate changes in quantities of myeloid derived suppressor cells (MDSCs), defined as CD14+HLA-DR^{low} cells, and T_{reg} cells, defined as CD4+FOX3P+ cells, throughout treatment
- To evaluate nCounter immune profiling of the tumor before treatment
- To explore tumor neoepitopes and mutational burden via whole gene and exome sequencing on pre-treatment tumor biopsy and correlation with clinical response
- To stratify clinical response rate by PD-L1 expression on pre-treatment biopsies
- To evaluate the tumor immune microenvironment on pre- and on-treatment tumor biopsies.

5.2 Study Endpoints

5.2.1 Primary Endpoint

The primary endpoint of this study is the response to combination ipilimumab/nivolumab and Ipilimumab alone at Week 18 defined as having achieved a complete response or partial response (PR) as measured by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria or a PR/complete response at any time prior to Week 18.

5.2.2 Secondary Endpoints

The secondary endpoints are as follows:

- Disease control rate (DCR) by RECIST v1.1 criteria of overall tumor burden at Week 12 and Week 18. DCR is defined as participants who achieve stable disease (SD), PR or complete response.
- Time to treatment failure and OS up to two years
- Safety and tolerability measured via metrics such as laboratory tests, vital signs, physical examinations as well as toxicity as graded by Common Terminology Criteria for AEs (CTCAE) v4.0.

5.2.3 Exploratory Endpoints

The exploratory endpoints of this study are as follows:

- All research samples for exploratory endpoints will be analyzed at a Parker Institute for Cancer Immunotherapy selected testing center. Please see Appendix 3 for further information
- Peripheral lymphocyte phenotype changes throughout treatment, including T_{reg} cells, defined as CD4+FOX3P+ cells, will be expressed using descriptive statistics at pre and post treatment time points. These will be assessed via flow cytometry of peripheral blood mononuclear cells (PBMCs).
- Changes in quantities of MDSCs, defined as CD14+HLA-DR^{low} cells, throughout treatment will be expressed using descriptive statistics at pre and post treatment time points.

- nCounter immune profiling of the tumor before treatment will be expressed using descriptive statistics at pre and post treatment time points and will be correlated with clinical response also using logistic regression models.
- Tumor neoepitopes and mutational burden will be correlated with clinical response also using logistic regression models.
- Summary statistics will be generated and differences between mutation burden or neo-antigen score as they relate to PD-L1 expression.
- Immunohistochemistry (IHC) will be used to assess PD-L1 expression on both immune cells and tumor cells. PDL-1 expression will be assessed pretreatment and on-treatment. A participant will be PD-L1 + if >1% of cells express PD-L1. If response data permit, the tumor positivity of PD-L1 expression will be compared in the pre- and post-treatment biopsies using a Wilcoxon signed rank test.
- Pre- and on- treatment PD-L1 expression and will be correlated with clinical response also using logistic regression models.
- IHC will be used to quantify cytotoxic and T_{regs}, including stains for CD3, CD4, CD8, FOXP3, ICOS and Lag3. Associations from pre to post treatment will be assessed using the Wilcoxon signed rank test for paired comparisons (e.g., the continuous measure, density of cells per high powered field).

6 INVESTIGATIONAL PLAN

6.1 Description of Overall Study Design and Plan

This is a multi-center, randomized, Phase 2 study of ipilimumab vs ipilimumab plus nivolumab in participants previously treated with a PD-1 inhibitor by Week 18 of therapy.

There will be 2 treatment arms in this study.

Arm A: Participants will receive combination checkpoint blockade with ipilimumab and nivolumab.

Arm B: Participants in this arm will receive ipilimumab alone.

A Simon 2-stage design will be implemented in each arm, allowing for early stopping for futility. Participants who are eligible will be required to have a pre-treatment biopsy and then will be randomized to either ipilimumab alone or ipilimumab in combination with nivolumab. Participants will be required to have an on-treatment biopsy within 14±5 days of their first dose of treatment. Participants will receive treatment for up to 4 cycles followed by observation phase.

The primary objective is to determine the response rate of combination ipilimumab/nivolumab and ipilimumab alone in participants previously treated with a PD-1 inhibitor by Week 18 of therapy. The total planned accrual is 12 participants in each arm. Participants will be assessed for the primary endpoint at 18 weeks. They will then be followed for TTF and OS for up to 2 years.

Secondary objectives include assessment of tolerability of ipilimumab and combination checkpoint blockade in previously treated participants as well as assessment of OS and time to treatment failure.

6.1.1 Study duration

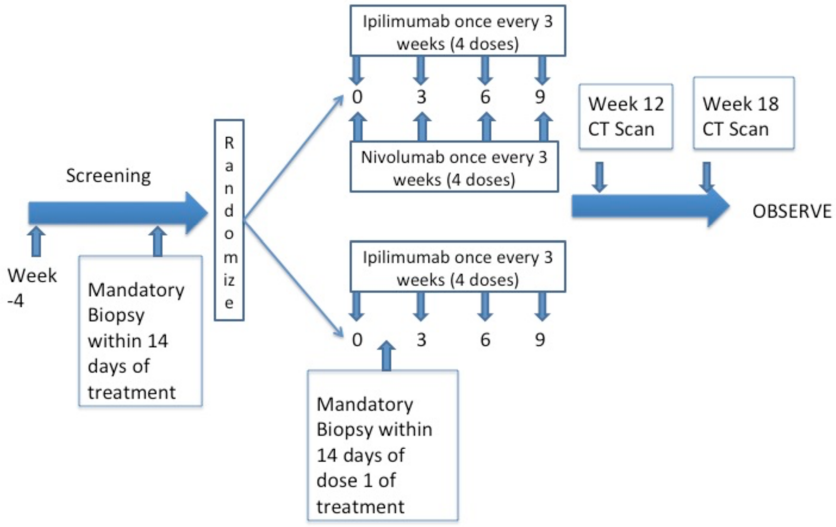
Participants on both arms will receive treatment for up to 4 cycles and then be observed for up to 2 years. After 2 years, all participants will go off study.

6.1.2 Randomization

Randomization will be managed centrally using an interactive voice response (IVR) system. Participants will be randomized following their pre-treatment biopsy at Screening/Baseline Visit. Participants will be stratified based on their previous response to PD-1 therapy (primary refractory vs progressive disease) and melanoma subtype. The primary refractory and progressive disease cohorts are defined in Section 7.1 (inclusion criteria number 4).

Figure 6 illustrates randomization schema:

Figure 6: Simplified randomization schema



Note: The on-treatment biopsy has a window of ±5 days.

6.2 Discussion of Study Design

This is a multi-center, randomized, parallel single arm, 2-stage Phase 2 study of ipilimumab and combined checkpoint blockade with ipilimumab and nivolumab in participants with unresectable Stage III or Stage IV melanoma who have previously received monotherapy with a PD-1 inhibitor with progression of disease or relapsed disease.

Checkpoint blockade has emerged as an effective therapeutic strategy for participants with advanced stage melanoma. Checkpoint inhibitors enhance antitumor immunity by blocking negative regulators of T-cell function that exist both on immune cells and on tumor cells. There are two classes of checkpoint blockade currently FDA approved, CTLA-4 antibodies and PD-1 antibodies. Ipilimumab blocks CTLA-4 and nivolumab is a PD-1 antibody. In this study, participants will be administered ipilimumab both as a single agent and in combination with nivolumab to explore whether dual checkpoint blockade synergy is as active in a pre-treated population as in a treatment-naïve population.

A total of 24 participants will be enrolled in this study. All participants will be followed up to 2 years after receiving the last dose of study drug.

7 SELECTION AND WITHDRAWAL OF PARTICIPANTS

Participants will be recruited by their medical, surgical, and radiation oncologist who encounter them in the clinical setting. The clinical trial will be listed on the clinicaltrials.gov website and on the institution's website. Participants will be identified through internal referrals and external referrals by Medical and Surgical Oncologists nationally and internationally. Participants will also be approached by the institution's co-investigators. Every effort will be made to maximize recruitment of participants, including women and minorities. The target population of participants include those who have previously received monotherapy with a PD-1 inhibitor with progression of disease or relapsed disease. Participants must meet the inclusion and exclusion criteria; no exceptions will be made for enrollment.

7.1 Inclusion Criteria

All participants must meet all of the following criteria at screening and baseline to participate in the study:

1. AJCC (2009) Stage IV cutaneous melanoma or Stage III cutaneous, acral or mucosal melanoma that is judged inoperable. Participants with a history of uveal melanoma are not eligible.
2. Measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm with conventional techniques or as >10 mm with computerized tomography (CT) scan. Participants must have at least one measurable lesion by RECIST and a separate lesion amenable to biopsy.
3. Histologic proof of melanoma reviewed and confirmed by the enrolling site.
4. Previous treatment with a PD-1 or PD-L1 inhibitor with documented progression of disease on most recent CT scan. Progression of disease is defined as 1) the appearance of a new measurable lesion (>10 mm) on cross-sectional imaging or physical examination OR 2) enlargement of previously detected lesions on two consecutive imaging studies OR 3) enlargement of a previously detected lesion with correlative symptomatology on one cross-sectional imaging study. Participants remain eligible if they had a previous response to a PD-1 inhibitor, including participants who had a complete response, PR or SD. Any participant who had refractory or relapsed disease is eligible for study enrollment. Treatment populations are defined in Section 12.
5. Participants who received adjuvant PD-1 therapy who then develop measurable disease are eligible. However, they must have received their last dose of PD-1/PD-L1 blockade within two months of enrollment in this study. They will be stratified with participants who have primary progressive disease.
6. Life expectancy of greater than 3 months.
7. Age ≥ 18 years old.
8. ECOG performance status = 0 or 1 or Karnofsky Performance Status equivalent
9. Participants must have adequate organ and marrow function as defined below:
   a. White blood cells (WBC) >2, 000/mcL
   b. Absolute neutrophil count >1,500/mcL
   c. Platelets >100,000/mcL

d. Hemoglobin > 9.0 g/dL
e. Total bilirubin ≤ 1.5 X institution's upper limit of normal
f. Aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase)/alanine aminotransferase (ALT) (serum glutamic pyruvic transaminase) ≤ 2.5 X institution's upper limit of normal for participants with no concurrent liver metastases, OR≤ 5 X institution's upper limit of normal for participants with concurrent liver metastases
g. Serum creatinine < 1.5x OR creatinine clearance of at least 40

10. Women of childbearing potential must have a negative serum pregnancy test within 24 hours prior to the start of study drug. A woman of childbearing potential is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over age 50 in the absence of other biologic or physiologic causes.
11. Women with child bearing potential and men with reproductive potential must be willing to practice acceptable methods of contraception.
12. Ability to understand and the willingness to sign a written informed consent document.
13. Willingness to undergo biopsy of metastatic site or site of unresectable disease prior to randomization.

7.2 Exclusion Criteria

Participants meeting any of the following criteria are ineligible to participate in this study:

1. Concurrent malignancies:
   a. Participants with a previously treated malignancy are eligible to participate if all treatment of that malignancy was completed at least 2 years before registration and the participant has no evidence of disease.
   b. Participants who have a concurrent malignancy that is clinically stable and does not require tumor-directed treatment are eligible to participate if the risk of the prior malignancy interfering with either safety or efficacy endpoints is very low (with agreement from the sponsor and PI).
   c. Other malignancies may be permitted if the risk of the prior malignancy interfering with either safety or efficacy endpoints is very low (with agreement from the sponsor and PI).
2. Any major surgical procedures or external beam radiotherapy within 14 days prior to study drug administration.
3. Use of other investigational drugs within 28 days prior to study drug administration.
4. Symptomatic or untreated leptomeningeal or brain metastases or spinal cord compression. Treated brain metastases must have been stable for at least 1 month and require treatment with less than 10 mg/day prednisone equivalent for at least two weeks prior to study drug administration.
5. Prior exposure to either ipilimumab or combined checkpoint blockade.
6. Any diagnosis of autoimmune disease. Participants with Type I diabetes mellitus, hypothyroidism only requiring hormone replacement, adrenal insufficiency on replacement dose steroids, skin disorders (such as vitiligo, psoriasis or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
7. Pregnant women and lactating women.

8. History of uveal melanoma.
9. Known Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection (with the exception of chronic or cleared HBV or HCV infection, which will be allowed). Once-documented negative result for HIV, HBV, and HCV is sufficient.
10. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection and psychiatric illness/social situations that would limit compliance with study requirements.
11. Participants with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement steroid doses >10 mg daily prednisone equivalent are permitted.
12. Participants with history of any grade 4 toxicity during previous anti PD-1 treatment or history of Grade 3 or higher pneumonitis.
13. Participants with a history of grade ≥2 neuropathy.
14. Prisoners or participants who are involuntarily incarcerated.
15. Children under the age of 18.
16. Participants who require hemodialysis.
17. Participants with a history of allergy to study drug components or history of a severe hypersensitivity reaction to any monoclonal antibody.

7.3 Withdrawal, Removal, and Replacement of Participants

A participant may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- Progression of disease: Either unequivocal symptomatic progression necessitating a change in therapy in the opinion of the treating physician or radiologic progression as defined by cross-sectional imaging utilizing RECIST 1.1 criteria.
- Treatment Cessation: Discontinuation criteria apply for all drug-related AEs attributed to nivolumab, ipilimumab or both. Treatment with all study drugs should be permanently discontinued for the following:
  - Any Grade 2 drug related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
  - Any Grade 3 non-skin, drug-related AE, with the following exceptions:
    - Grade 3 diarrhea lasting <7 days
    - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except
      - Grade 3 drug-related thrombocytopenia >7 days or associated with bleeding requires discontinuation
      - Any drug-related liver function test abnormality that meets the following criteria requires discontinuation:
        - AST or ALT >8 x upper limit of normal (ULN)
        - Total Bilirubin >5x ULN
        - Concurrent AST or ALT and total bilirubin >2x ULN
  - Any Grade 4 drug-related AE or laboratory abnormality, except for the following events which do not require discontinuation.

- Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis.
- Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset

  - Any dosing interruption lasting >6 weeks with the following exceptions:
    - Dosing interruptions to allow for prolonged steroid tapers to manage drug-related AEs are allowed.
    - Dosing interruptions >6 weeks that occur for non-drug related may be allowed if approved by the primary Investigator
  - Any AE, laboratory abnormality or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued drug dosing.

- Withdrawal of consent: Participant may withdraw consent at any time.
- Death
- Screening Failure: If, at any point after enrollment, the PI determines that the participant does not meet all inclusion criteria or meets any exclusion criteria. Rescreening is permitted.

7.4 Follow-Up for Drug Discontinuation/Participant Withdrawal from Study

If a participant discontinues study treatment and is withdrawn from the study for any reason, the study site must immediately notify the medical monitor. The date and the reason for study discontinuation must be recorded on the electronic case report form (eCRF). Participants who withdraw prematurely are to attend an Early Termination Visit, if possible, and complete all assessments.

In the event that a participant discontinues prematurely from the study due to a treatment-emergent adverse events (TEAE) or serious TEAE, the TEAE or serious TEAE will be followed until it resolves (returns to normal or baseline values) or stabilizes, or until it is judged by the Investigator to be no longer clinically significant.

Once a participant is withdrawn from the study, the participant may not re-enter the study.

8 TREATMENTS

Participants will be screened for enrollment. If they meet all inclusion criteria and do not meet exclusion criteria, they will be referred for pre-treatment biopsy of either an unresectable lesion or a metastatic lesion. After biopsy, each participant will be randomized either to Arm A (combination ipilimumab and nivolumab) or Arm B (ipilimumab alone).

Arm A:

- Participants will be required to start treatment within 14 days of their pre-treatment biopsy. The pre-treatment biopsy is considered standard of care.
- One dose of ipilimumab and nivolumab administered together constitutes one cycle; they will be administered in the manner described in Section 8.4.
- Cycles will be administered every 21 days±4 days for up to 4 cycles.

- CT scans will be administered at weeks 12 and 18 and every 12 weeks for up to 2 years after study treatment begins. These are considered standard of care.
- Blood will be drawn at every cycle during treatment and during follow-up visits. Standard bloodwork, such as complete blood count (CBC) and comprehensive metabolic panel (CMP), are part of routine care. Other bloodwork (approximately 40 mL) will be drawn which is solely for the purpose of research.
- An on-treatment biopsy will be required within 14 days ± 5 days of the start of Cycle 1. This is solely for the purpose of research. All reasonable efforts will be made to biopsy the same lesion pre- and on-treatment.

Arm B:

- Participants will be required to start treatment within 14 days of their pre-treatment biopsy. The pre-treatment biopsy is considered standard of care.
- One dose of ipilimumab constitutes one cycle; it will be administered in the manner described in Section 8.4.
- Cycles will be administered every 21±4 days for up to 4 cycles.
- CT scans will be administered at weeks 12 and 18 and every 12 weeks for up to 2 years after study treatment begins. These are considered standard of care.
- Blood will be drawn at every cycle during treatment and during follow-up visits. Standard bloodwork, such as CBC and CMP, are part of routine care. Other bloodwork (approximately 40 mL) will be drawn which is solely for the purpose of research.
- An on-treatment biopsy will be required within 14 days ± 5 days of the start of Cycle 1. This is solely for the purpose of research. All reasonable efforts will be made to biopsy the same lesion pre- and on-treatment.

Basic information about the study treatments is provided in Table 2.

Table 2: Details of Study Treatments/Intervention

Product Description					
Product Description and Dosage Form	**Potency**	**Primary Packaging (Volume)/ Label Type**	**Secondary Packaging (Qty) /Label Type**	**Appearance**	**Storage Conditions (per label)**
Nivolumab BMS-936558-01 Solution for Injection[a]	100 mg (10 mg/mL)	10 mL vial	5-10 vials per carton/ Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect form light and freezing
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	40 mL vial	4 vials per carton/Open-label	Clear, colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect from light and freezing.

a Nivolumab may be labeled as BMS-936558-01 Solution for Injection

If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab and ipilimumab include laboratory coats and gloves. Please see Appendix 1 for further information.

Storage Conditions and Handling:

Ipilimumab injection may be stored undiluted, 200 mg/vial (5 mg/mL), or following dilution to concentrations between 1 mg/mL and 4 mg/mL in 0.9% Sodium Chloride Injection (USP), or 5% Dextrose Injection (USP) in PVC, non-PVC/ or glass containers for up to 24 hours in the refrigerator (2°C to 8°C) or at room temperature/room light. For longer storage, ipilimumab should be kept refrigerated (2°C to 8°C) with protection from light.

Ipilimumab injection must not be frozen.

Partially used vials or empty vials of Ipilimumab Injection should be discarded at the site according to appropriate drug disposal procedures.

8.1 Details of Study Treatments/Intervention

8.1.1 Ipilimumab

Mechanism of Action: CTLA-4 is a negative regulator of T-cell activity. Ipilimumab is a monoclonal antibody that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 augments T-cell activation and proliferation, including the activation and proliferation of tumor infiltrating T-effector cells. Inhibition of CTLA-4 can also reduce T-regulatory cell function, which may contribute to a general increase in T cell responsiveness, including the anti-tumor immune response.

Storage and formulation: Ipilimumab currently comes packaged in a concentrated form in either a 50 mg (5 mg/mL) or 200 mg (5 mg/mL) single use vial. This concentrated solution should be diluted with 0.9% Sodium Chloride or 5% Dextrose Injection to prepare a diluted

solution with a final concentration ranging from 1 mg/mL to 2 mg/mL. Ipilimumab must be stored at 2°-8°C. Vials should be protected from light and should not be frozen.

Pharmacokinetics: The pharmacokinetics of ipilimumab were studied in 785 patients with unresectable or metastatic melanoma who received doses of 0.3, 3, or 10 mg/kg once every three weeks for 4 doses. Peak concentration (C_{max}), trough concentration (C_{min}), and area under the plasma concentration versus time curve (AUC) of ipilimumab increased dose proportionally within the dose range examined. Upon repeated dosing every 3 weeks, the clearance (CL) of ipilimumab was found to be time-invariant, and systemic accumulation was 1.5-fold or less. Steady-state concentrations of ipilimumab were reached by the third dose; the mean C_{min} at steady-state was 19.4 mcg/mL following repeated doses of 3 mg/kg. The mean value for terminal half-life was 15.4 days and for CL was 16.8 mL/h.

Administration: Ipilimumab will be mixed, stored and administered as per commercial guidelines.

8.1.2 Nivolumab

Mechanism of Action: Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T-cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occur in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Nivolumab is a human immunoglobulin G4 monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing the PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response.

Storage and formulation: Nivolumab currently comes packaged in a concentrated form in either a 40 mg (10 mg/mL) or 100 mg (10 mg/mL) single use vial. This concentrated solution should be diluted with 0.9% Sodium Chloride or 5% Dextrose Injection to prepare a diluted solution with a final concentration ranging from 1 mg/mL to 10 mg/mL. Nivolumab must be stored at 2°-8°C. Vials should be protected from light and should not be frozen.

Pharmacokinetics: The pharmacokinetics of nivolumab was studied in 909 patients over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses every 2 or 3 weeks. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. The mean CL is 9.5 mL/h and mean elimination half-life is 25.7 days. Steady-concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks and systemic accumulation was approximately 3-fold.

Administration: Nivolumab will be mixed, stored and administered as per commercial guidelines.

8.2 Toxicities / Side Effects

8.2.1 Ipilimumab

Likely Side Effects: Diarrhea, inflammation of the colon (colitis), increase in liver enzymes, fatigue, skin itchiness, skin rash, nausea, abdominal pain, decreased appetite, fever, vomiting, headache, constipation, adrenal gland abnormalities, and thyroid gland abnormalities.

Less Likely Side Effects: Chills, weakness, muscle pain, and redness of skin.

Rare Side Effects: Decrease or total loss of hormones of pituitary gland, allergic reactions, inflammation of the liver, inflammation of the pituitary gland, decreased red blood cells, loss of color (pigment) from areas of skin, decreased or blurry vision, or inflammation of the eye, numbness or tingling in your fingers or toes, inflammation or loss of the lining of the brain or spinal cord, inflammation of the kidneys, and joint pain.

8.2.2 Ipilimumab and Nivolumab

Likely Side Effects: Diarrhea, inflammation of the colon (colitis), increase in liver enzymes, fatigue, swelling of the extremities, flu-like feeling, pain, skin itchiness, skin rash or xerosis (increased dryness), vitiligo (loss of pigment or color in the skin), nausea, abdominal pain, decreased appetite, fever, vomiting, constipation, flatulence, dry mouth, weight loss, cough, shortness of breath, headache, peripheral neuropathy (numbness or tingling of the fingers or toes), dizziness, change in sensation of taste, joint pain or stiffness, dehydration, increased blood sugar, low sodium levels, infections, inflammation of the optic disc, low blood pressure, and difficulty sleeping.

Less Likely Side Effects: inflammation of the pancreas, decreased movement of the intestines, inflammation of the thyroid, lung inflammation (pneumonitis), shortness of breath, joint swelling, muscle soreness, weakness, stiffness, or spasm, adrenal gland abnormalities, inflammation of the heart or lining of the heart, acute kidney injury or failure, and increase in inflammatory blood proteins.

Rare Side Effects:

- Myasthenia gravis, a nerve disease that may cause weakness of the eye, face, breathing and swallowing muscles. One death in a patient who received the combination was considered due to myasthenia gravis and severe infection (sepsis)
- A syndrome associated with fever, WBC activation and abnormal function (including destruction of other blood cells by WBCs), low blood cell counts, rash, and enlargement of the spleen.

8.3 Treatment of Nivolumab or Ipilimumab Related Infusion Reactions

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms.

All Grade 3 or 4 infusion reactions should be reported as an serious adverse event (SAE) if criteria are met. Infusion reactions should be graded according to National Cancer Institute (NCI) CTCAE 4.00 guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate:

For Grade 1 symptoms: infusion interruption not indicated; intervention not indicated

Remain at bedside and monitor participant until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg at least 30 minutes before additional nivolumab administrations.

For Grade 2 symptoms: requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, intravenous [IV] fluids); prophylactic medications indicated for 24 hours.

Stop the nivolumab or ipilimumab infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen 325 to 1000 mg; remain at bedside and monitor participant until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur then no further nivolumab or ipilimumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the participant until resolution of symptoms. The amount of study drug infused must be recorded on the eCRF. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg should be administered at least 30 minutes before additional nivolumab or ipilimumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: Grade 3: prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates). Grade 4: life threatening; pressor or ventilatory support indicated.

Immediately discontinue infusion of nivolumab or ipilimumab. Begin an IV infusion of normal saline, and treat the participant as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Participant should be monitored until the Investigator is comfortable that the symptoms will not recur. Nivolumab or ipilimumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

8.4 Intervention

8.4.1 Dosage and administration

Both nivolumab and ipilimumab will be stored, mixed and administered as per published commercial guidelines (please see Appendix 1). For participants in the combination arm, nivolumab will first be administered intravenously at a dose of 1 mg/kg of body weight over a period of approximately 60 minutes, once every 3 weeks for 4 doses. Approximately 30 minutes after the completion of each nivolumab infusion, participants will receive 3 mg/kg of ipilimumab over a period of approximately 30 minutes.

In the ipilimumab monotherapy group, participants will receive 3 mg/kg of ipilimumab over a period of approximately 30 minutes once every 3 weeks for 4 doses.

8.4.2 Monitoring and Dose Delay Criteria

Participants should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and laboratory test values are acceptable. If toxicity occurs as indicated below, participants in both study arms should have study drug(s) held. In participants who are in the combined treatment arm, both drugs should be held for any toxicity. Dose delays are designed to maximize treatment for those who derive clinical benefit from treatment while ensuring participant safety. Participants should follow timed assessments, and continuation on study is at the PI's discretion.

Nivolumab and/or ipilimumab administration should be delayed for the following reasons:

- Grade ≥2 non-skin, drug-related AEs with the following exceptions:
    - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Any Grade 3 skin, drug-related AE
- Any Grade 3 drug-related laboratory abnormalities with the following exceptions for lymphopenia, leukopenia, AST, ALT or total bilirubin
    - Grade 3 lymphopenia or leukopenia does not require dose delay
    - If a participant has a baseline AST, ALT or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥2 toxicity
    - If a participant has a baseline AST, ALT or total bilirubin that is within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥3 toxicity
- Any AE, laboratory abnormalities, or intercurrent illness, which in the judgment of the Investigator warrants delaying the dose of study drug.

8.4.3 Management Algorithms for Immune-related Adverse Events

Immuno-oncology agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Immune-related AEs will be managed as per published guidelines. Please see Appendix 2 for further details.

8.4.4 Dose Modifications

Nivolumab and ipilimumab dose reductions and escalations are not permitted in either study arm.

8.4.5 Criteria to Resume Treatment

Criteria to resume treatment apply for all drug-related AEs attributed to nivolumab, ipilimumab or both. Participants may resume treatment with study drug(s) when the drug-related AEs resolve to Grade ≤1 or baseline value with the following exceptions:

- Participants may resume treatment in the presence of Grade 2 fatigue
- Participants who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment
- See Appendix 2 for detailed management algorithms of irAEs

8.5 Blinding

Not Applicable.

8.6 Treatment Accountability and Compliance

Administration of study drugs will be supervised by study personnel or assigned infusion room nursing staff, who will monitor compliance. Study drugs accountability will be maintained in the Pharmacy Source documents i.e. accountability logs or in the study master file, as required.

9 STUDY PROCEDURES

Table 3 outlines the timing of procedures, and assessments to be performed throughout the study. See Sections 9.1 to 9.2.3 for additional details of study procedures.

Table 3: Schedule of Assessments

	Baseline/ Screening[a]	Cycle 1[b]	Cycle 2	Cycle 3	Cycle 4	Follow-up Visit 1 and 2[d]	Additional Follow-up Visits[e]	Early Termination Visit[f]
Obtain Informed Consent	X							
Participant History	X							
Inclusion/Exclusion criteria	X							
Biopsy of Target Lesion[c]	X	X						
Prior/concomitant medications	Collected from Screening to Follow-up							
Physical Examination	X	X	X	X	X	X		X
Performance status	X	X	X	X	X	X		X
Height/Weight	X	X	X	X	X	X		X
Vital Signs	X	X	X	X	X	X		X
Complete Blood Count	X	X	X	X	X	X		X
Complete Metabolic Panel, LDH	X	X	X	X	X	X		X
Thyroid function testing[g]	X	X	X	X	X	X		X
Pregnancy test (serum)	X	X	X	X	X	X		X
HCV, HBV, HIV Testing	X							
CT scan[h]	X				X	X		X
MRI Brain	X							
ECG	X							
Adverse Events	Collected from consent to 100 days after drug discontinuation							
Drug Administration		X	X	X	X			
Research blood (~40mL)	X	X	X	X	X	X		X

PD-L1 expression on banked tumor specimen if available	X							
Survival Data						X	X	X

[a]Screening assessments are recommended to be performed within 28 days prior to treatment unless otherwise specified above

[b]Each cycle=21 days±4 days

[c]Biopsy at baseline for all participants within 14 days of Cycle 1, Day 1. On-treatment biopsy must be performed within 14 days±5 days of first dose of study drug.

[d]Follow up period begins when the last dose of study therapy is administered. Follow-up visit 1=21 days from last dose ± 7 days. Follow-up visit 2=42 days from last dose ± 7 days. If the participant completed follow-up visit 1 and follow-up visit 2 and *has* progressed, the participant is not required to have scans every 12 weeks. Survival could be assessed via calls every 3 months (±7 days). If a participant is off treatment and *has not* progressed, they would continue to visit the site and have scans every 12 weeks.

[e]Additional follow-up visits will be scheduled every 3 months ±7 days. For participants who end treatment for toxicity, scans should continue every 12 weeks until progression of disease. After progression of disease, survival calls will occur every 3 months (±7 days).

[f]For participants who terminate the study early, follow-up will begin 21 days from the last dose (follow-up visit 1).

[g]TSH will be checked at every visit and will reflex to check free T4 if abnormal.

[h]Per standard of care to provide data for RECIST measurements as appropriate for each participant per the investigator physician. CT scans will be performed at baseline (-7 days), Week 12, Week 18, and every 12 weeks (±7 days) thereafter until progression of disease, death, or end of study for up to 2 years. A CT scan of the chest, abdomen and pelvis or an MRI of the abdomen and pelvis plus a non-contrast CT of the chest are acceptable.

9.1 Participant Informed Consent

Prior to performing any study-related procedures, the Investigator (or his/her designated staff member) will obtain written informed consent from the participant. After informed consent is obtained, the participant will be registered on study and begin "Screening/Baseline" evaluation. They will be monitored for AEs and clinical progression. They will continue to be followed periodically utilizing phone, email, fax, or postal mail for OS data for up to 2 years.

9.2 Procedures by Study Visit or Period

9.2.1 Pretreatment Evaluation

The following procedures and assessments must be performed prior to treatment start. All intervals are defined with respect to Cycle 1, Day 1 of treatment.

9.2.1.1 At any time prior to the start of the study drug

- Histologic confirmation of melanoma by the institution's pathologist.

9.2.1.2 Within 4 weeks prior to the start of the study drug

- Written Informed Consent
- A contrast-enhanced CT or magnetic resonance imaging (MRI) of the brain as well as of the chest, abdomen and pelvis. A CT scan of the chest, abdomen and pelvis or an MRI of the abdomen and pelvis plus a non-contrast CT of the chest are acceptable.
- Electrocardiogram (ECG)

9.2.2 Within 2 Weeks Prior to the Start of the Study

- Updated medical history and physical examination including measurement of vital signs and ECOG performance status
- Medication review
- Complete blood count, comprehensive metabolic panel, thyroid stimulating hormone (TSH) and free T4
- HIV enzyme-linked immunosorbent assay, HBV Core antibody, HBV surface antigen, HCV antibody. HIV consent will be obtained and documented as per the institution's guidelines.
- Serum beta-human chorionic gonadotropin for women of child-bearing potential (defined as women less than 55 years of age)
- Fresh core biopsy of target lesion that obtains a goal of 4 adequate cores, with 2-3 considered acceptable or excisional biopsy.

9.2.3 Unscheduled Visits

The Investigator may at his/her discretion arrange for a participant to have an unscheduled assessment, especially in the case of AEs that require follow-up or an AE considered by the Investigator to be possibly related to the use of study drug. The unscheduled visit page in the eCRF must be completed.

10 EFFICACY ASSESSMENTS

10.1 Response in Solid Tumor Criteria 1.1

10.1.1 Definitions of Measurable Disease

Measurable disease is defined as at least 1 target lesion, i.e. one that can be accurately measured in at least 1 dimension (longest dimension to be recorded). Each lesion must be 10 mm in 1 short axis as measured on CT or MRI; lymph nodes must be at least 15 mm in short axis.

10.1.2 Target" and "Non-Target" lesions

10.1.2.1 Target Lesions

All measurable lesions up to a maximum of 5 lesions representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest dimension) and their suitability for accurate repetitive measurements.

A sum of the longest dimension (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

10.1.2.2 Non-Target Lesions

All other lesions or sites of disease should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present" or "absent".

10.1.2.3 Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

10.1.3 Baseline Evaluation

Baseline disease status should be assessed with cross-sectional imaging (CT with contrast preferred) as close as possible to the start of therapy and never more than 28 days before the beginning of therapy. If iodinated contrast dye is contraindicated, an MRI with gadolinium may substitute for the abdomen and pelvis, but a CT chest without contrast must also be performed.

10.1.4 Repeat Evaluations

Repeat Evaluations are periodic measurements of disease burden must be assessed utilizing the same cross-sectional imaging modalities as baseline. Participants who do not undergo

repeat assessments within acceptable time frames will be removed from study and censored at the time of last evaluation.

10.1.5 Best Response

- Complete Response (CR): Disappearance of all target and non-target lesions and no evidence of new lesions documented by 2 disease assessments at least 4 weeks apart.
- Partial Response (PR): At least a 30% decrease in the in the longest dimension (LD) of all target lesions, taking as reference the baseline sum LD. There can be no unequivocal progression of non-target lesions and no new lesions. Documentation by 2 disease assessments at least 4 weeks apart is required.
- Progressive Disease (PD): At least a 20% increase in the sum of LD of target lesions, taking as reference the smallest sum LD or the appearance of new lesions within 8 weeks of study entry. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
- Stable Disease (SD): Any condition not meeting the above criteria.
- Inevaluable for response is defined as having no repeat tumor assessments following initiation of study therapy for reasons unrelated to symptoms or signs of disease.

10.2 Quantifying Clinical Correlates of Response

Outcome will be assessed as follows:

- Objective Response Rate (ORR): The proportion of participants with either (1) CR or (2) PR by RECIST 1.1 criteria.
- Survival: The observed length of life from first dose of study drug to death or the date of last contact.
- TTF: Is defined as the time from first study drug treatment until the participant is started on another line of systemic therapy or participant death, whichever occurs first. Participants who are alive and do not start another therapy will be censored at the time of last follow-up.

11 SAFETY ASSESSMENTS

Safety assessments (vital signs, physical examinations, performance status, height/weight, ECG recording, AEs, clinical laboratory results (routine hematology and biochemistry, and CT and MRI scans) are to be performed at protocol specified visits, as specified in the Schedule of Assessments, Table 3.

11.1 Adverse Events

11.1.1 Definition of Non-serious Adverse Events

An AE is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant 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 (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

A non-serious AE is an AE not classified as serious.

The collection of non-serious AE information will begin at initiation of study drug. All non-serious AEs (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

The causal relationship to study drug is determined by a physician and should be used to assess all AE. The casual relationship can be one of the following:

UNRELATED: This category applies to those AEs that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.).

UNLIKELY: This category applies to those AEs that are judged to be unrelated to the test drug, but for which no extraneous cause may be found. An AE may be considered unlikely to be related to study drug if or when it meets 2 of the following criteria: (1) it does not follow a reasonable temporal sequence from administration of the test drug; (2) it could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it does not follow a known pattern of response to the test drug; or (4) it does not reappear or worsen when the drug is re-administered.

POSSIBLY: This category applies to those AEs for which a connection with the test drug administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; or (3) it follows a known pattern of response to the test drug.

PROBABLY: This category applies to those AEs that the investigator feels with a high degree of certainty are related to the test drug. An AE may be considered probably related if or when it meets 3 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose (note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; for example, as in bone marrow depression, fixed drug eruptions, or tardive dyskinesia); or (4) it follows a known pattern of response to the test drug.

DEFINITELY: This category applies to those AEs that the investigator feels are incontrovertibly related to test drug. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose and recurs with re-exposure to drug (if rechallenge occurs); and (4) it follows a known pattern of response to the test drug.

Classification of AEs by intensity should also be determined by a physician.

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

11.1.2 Serious Adverse Events

An AE is considered serious if it results in any of the following outcomes:

- Death
- A life-threatening AE
- An AE that results in hospital admission or prolongation of existing hospitalization

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the participant or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition
- Potential drug induced liver injury (DILI) is also considered an important medical event. DILI is defined as the following:
    - ALT or AST elevation >3x ULN AND
    - Total bilirubin >2x ULN, without elevated serum alkaline phosphatase AND
    - No other immediately apparent possible causes of AST/ALT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via study drug is an SAE.

Although pregnancy, overdose, and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

Note: Hospital admission for elective pre-planned surgeries is not considered an SAE.

Disease Progression is considered a non-reportable event.

SAE reporting is required as soon as the participant signs consent and is registered. SAE reporting is required for 100-days after the participant's last investigational treatment or intervention. Any events that occur after the 100-day period and that are at least possibly related to protocol treatment must be reported.

inVentiv Health Clinical will manage SAEs using ARGUS, and all sites will send reports to inVentiv's safety team via email. Sites will not upload any reports directly into ARGUS.

SAE Reporting to BMS and inVentiv

Following the participant's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All AEs are to be followed until resolution, until a stable clinical endpoint is reached, or for 100 days after the last dose of study treatment, unless other anticancer therapy is initiated.

All SAEs must be collected that occur during the screening period. If applicable, SAEs must be collected that relate to any protocol-specified procedure (e.g., a follow-up skin biopsy). The Investigator should report any SAE that occurs after these time periods that is believed to be related to study drug or protocol-specified procedure.

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.)

Sites should complete SAE reports and then submit the reports per their local IRB requirements.

All SAEs should be followed to resolution or stabilization.

The Sponsor will ensure that all SAEs in the clinical database are reported to BMS and any applicable health authority during the conduct of the study.

11.1.3 Pregnancy

Female participants of childbearing potential must have a negative pregnancy test at Screening. An acceptable form of contraception must be used for up to 5 months post last dose by all female participants and for 7 months post last dose by all male participants (as detailed in Appendix 4). Following administration of study drug, any known cases of pregnancy in female participants will be reported until the participant completes or withdraws from the study. The pregnancy will be reported immediately by phone and by faxing/emailing a completed Pregnancy Report to the Sponsor (or designee) within 24 hours of knowledge of the event. The Investigator will follow the participant until completion of the pregnancy and must assess the outcome in the shortest possible time but not more than 30 days after completion of the pregnancy. The Investigator should notify the Sponsor (or designee) of the pregnancy outcome by submitting a follow-up Pregnancy Report on a Pregnancy Surveillance Form. If the outcome of the pregnancy meets the criteria for immediate classification of an SAE (e.g., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator will report the event by phone and by faxing a completed SAE form to the Sponsor (or designee) within 24 hours of knowledge of the event.

11.1.4 Overdose

The Investigator must immediately notify the Sponsor of any occurrence of overdose with study drug. Overdose is defined as any dose higher than the dose specified to be administered in accordance with the protocol.

All overdoses should be reported to inVentiv as SAEs (see Section **Error! Reference source not found.**). Details of signs and symptoms, clinical management, and outcome should be reported, if available. Overdoses should also be captured as protocol deviations.

11.1.5 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

Progression of the cancer under study, including deaths, as judged by the Investigator, is not considered a reportable event. Any suspected endpoint, which upon review from the Investigator, is not considered progression of the cancer under study must be reported as an SAE. Within 24 hours of determination that the event is not progression of the cancer under study, an SAE form should be forwarded to InVentiv Pharmacovigilance Group as described (see Section **Error! Reference source not found.**).

All deaths will be recorded on the Death eCRF page.

11.2 Unanticipated Problems/Non-Compliance

Unanticipated Problems

An unexpected problem is any incident, experience, or outcome that meets all of the following criteria:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

An incident, experience, or outcome that meets the three criteria above generally will warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others. Examples of corrective actions or substantive changes that might need to be considered in response to an unanticipated problem include:

- changes to the research protocol initiated by the investigator prior to obtaining IRB approval to eliminate apparent immediate hazards to subjects;
- modification of inclusion or exclusion criteria to mitigate the newly identified risks;
- implementation of additional procedures for monitoring subjects;
- suspension of enrollment of new subjects;
- suspension of research procedures in currently enrolled subjects;
- modification of informed consent documents to include a description of newly recognized risks; and
- provision of additional information about newly recognized risks to previously enrolled subjects.

Only a small subset of AEs occurring in human subjects participating in research will meet these three criteria for an unanticipated problem. Furthermore, there are other types of incidents, experiences, and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered AEs. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with AEs. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs.

It may be difficult to determine whether a particular AE is unexpected. This determination may require analysis of appropriate data on all subjects enrolled in the research. In addition, unanticipated problems may become apparent during continuing renewals, protocol violations,

deviations, complaints, injuries, or deaths. Investigators are required to promptly report to the IRB unanticipated problems involving risks to subjects or others. A report for an unexpected event should contain a clear explanation of why the event(s) was determined to be an unanticipated problem and a description of any proposed protocol changes or other corrective actions to be taken by the investigators in response to the unanticipated problem.

Non-Compliance

All investigators should comply with all applicable local, state, and federal regulations in the conduct of research involving human subjects. Non-compliance is defined as any violation of any regulation that governs human subject research, any deviation from the study protocol approved by the IRB, or any violation of any conditions imposed by the IRB on the approval of the study or conduct of the research. Investigators will also be informed when allegations of non-compliance are made during the study. Investigators are responsible for reporting in writing, all suspected incidents of non-compliance within 2 business days of discovery. Reports should be sent to inVentiv Health and the MSKCC research team for submission to the IRB and should include the incident, date of the incident, individuals involved, whether the incident requires further action, and corrective actions and procedures.

12 STATISTICAL ANALYSIS

A Statistical Analysis Plan (SAP) will be prepared after the protocol is approved. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will serve as a compliment to the protocol and supersedes it in case of differences.

The statistical evaluation will be performed using the Statistical Analysis Software (SAS®) Version 8.1 or higher (SAS Institute, Cary, NC). All data will be listed, and summary tables will be provided. Summary statistics will be presented by dose group. For continuous variables, data will be summarized with the number of participants (N), mean, standard deviation, median, minimum, and maximum by treatment group. For categorical variables, data will be tabulated with the number and proportion of participants for each category by treatment group.

12.1 Determination of Sample size

Twelve participants will be enrolled in each arm for a total of 24 participants. A response rate of 10% or less would not be considered promising (null hypothesis) as the ipilimumab response rate in untreated patients is 10.9%.[33] A response rate of at least 30% is promising (alternative hypothesis). Point estimates and 95% confidence intervals for the response rates will be reported. Alpha (probability of Type I error) for hypothesis tests will be 0.1. If 4 or more of 12 participants in an arm respond (response rate of 33% or greater), the treatment will be considered promising for further investigation.

12.2 Analysis Populations

Evaluable participants for efficacy

- All participants who receive at least 1 dose of study drug(s) will be evaluated for the primary endpoint. Participants who develop rapid symptomatic disease progression

or drop out early due to death will be treated as non-responders. Participants who develop early toxicities that require treatment delay or discontinuation will continue to be evaluable on study.

- Participants may be replaced in either arm if they complete randomization but do not complete any cycles of therapy.

Evaluable participants for toxicity

Participants who have completed at least one treatment cycle on either arm will be considered evaluable for toxicity.

12.3 Efficacy Analysis

12.3.1 Analysis of Primary Efficacy Endpoint

- The primary endpoint is objective response (CR and PR) as defined by RECIST criteria by Week 18. Objective response rates will be estimated as proportions with 95% CIs estimated using an exact procedure.

12.3.2 Analysis of Secondary Efficacy Endpoints

- DCR, defined as participants who achieve SD, PR or complete response at Week 12 and/or Week 18 as measured by RECIST v1.1 will be estimated as proportions with 95% CIs estimated using an exact procedure.
- Participants will be followed for duration of response (in those participants who derive clinical benefit), TTF and OS for two years; these will be estimated and demonstrated using Kaplan Meier approaches.

12.3.3 Analysis of Exploratory Efficacy Endpoints

- All research samples for exploratory endpoints will be analyzed at a Parker Institute for Cancer Immunotherapy selected testing center. Please see Appendix 3 for further information.
- Peripheral lymphocyte phenotype changes throughout treatment, including T_{reg} cells, defined as CD4+FOX3P+ cells, will be expressed using descriptive statistics at pre and post treatment time points. These will be assed via flow cytometry of PBMCs.
- Changes in quantities of MDSCs, defined as CD14+HLA-DR^{low} cells, throughout treatment will be expressed using descriptive statistics at pre and post treatment time points.
- nCounter immune profiling of the tumor before treatment will be expressed using descriptive statistics at pre and post treatment time points and will be correlated with clinical response also using logistic regression models.
- Tumor neoepitopes and mutational burden will be correlated with clinical response also using logistic regression models.
- Summary statistics will be generated and differences between mutation burden or neo-antigen score as they relate to PD-L1 expression

- IHC will be used to assess PD-L1 expression on both immune cells and tumor cells. PDL-1 expression will be assessed pre-treatment and on-treatment. A participant will be PD-L1 + if >1% of cells express PD-L1. If response data permit, the tumor positivity of PD-L1 expression will be compared in the pre- and post-treatment biopsies using a Wilcoxon signed rank test.
- Pre- and on- treatment PD-L1 expression and will be correlated with clinical response also using logistic regression models.
- IHC will be used to quantify cytotoxic and T_{regs}, including stains for CD3, CD4, CD8, FOXP3, ICOS and Lag3. Associations from pre to post treatment will be assessed using the Wilcoxon signed rank test for paired comparisons (e.g., the continuous measure, density of cells per high powered field).

12.4 Safety Analysis

Adverse events and toxicity data will be tabulated and summarized using descriptive statistics.

12.5 Data Review Team

The study will be closely monitored and data will be reviewed on an ongoing basis. In order to ensure the safety and well-being of participating subjects, as well as, the validity of data during the study, a Data Review Team (DRT) will review the safety and further emerging data on a regular basis. During these meetings, aggregated safety data and individual participant data derived from medical data listing reviews will be presented, reviewed, and discussed. The DRT team will consist of team members from the Sponsor, inVentiv, the Coordinating PI, and all active PIs.

13 STUDY MANAGEMENT

13.1 Approval and Consent

13.1.1 Regulatory Guidelines

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the Code of Federal Regulations (CFR), and in compliance with good clinical practice (GCP) guidelines.

13.1.2 Institutional Review Board/Independent Ethics Committee

Conduct of the study must be approved by an appropriately constituted Independent Ethics Committee (IEC)/IRB. Approval is required for the study protocol, investigational drug brochure, protocol amendments, informed consent forms (ICFs), and participant information sheets.

13.1.3 Informed Consent

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw

from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the CFR and the IRB/Privacy Board of this Center. The consent form will include the following:

- The nature and objectives, potential risks and benefits of the intended study.
- The length of study and the likely follow-up required.
- Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, participants will be offered an option of supportive care for therapeutic studies.)
- The name of the Investigator(s) responsible for the protocol.
- The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of participant privacy concerning research specific information. In addition to signing the IRB Informed Consent, all participants must agree to the Research Authorization component of the ICF.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed ICF.

13.2 Research Participant Registration

Participant eligibility will be confirmed as defined in the Sections 7.1 and 7.2. Informed consent will be obtained by following procedures defined in Section 13.1.3 entitled Informed Consent. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

Registrations must be submitted via the ALMAC Interactive Voice Response System.

13.3 Data Handling

A Study Coordinator (SC) or equivalent will be assigned to the study. The responsibilities of the SC include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized participant record.

Any data to be recorded directly on the eCRFs (to be considered as source data) will be identified at the start of the study. Data reported on the eCRF that are derived from source documents should be consistent with the source documents, or the discrepancies must be explained.

Clinical data will be entered on eCRFs for transmission to the Sponsor. Data on eCRFs transmitted via the web-based data system must correspond to and be supported by source documentation maintained at the study site, unless the study site makes direct data entry to the databases for which no other original or source documentation is maintained. In such cases, the study site should document which eCRFs are subject to direct data entry and should have in place procedures to obtain and retain copies of the information submitted by direct data

entry. All study forms and records transmitted to the Sponsor must carry only coded identifiers such that personally identifying information is not transmitted. The primary method of data transmittal is via the secure, internet-based electronic data capture (EDC) system maintained by inVentiv Health Clinical. Access to the EDC system is available to authorized users via the study's Internet web site, where an assigned username and password are required for access.

Any changes made to data after collection will be made through the use of Data Clarification Forms. eCRFs will be considered complete when all missing and/or incorrect data have been resolved.

13.4 Source Documents

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data or other activities in a clinical study necessary for the reconstruction and evaluation of the study.

13.5 Record Retention

Study records and source documents must be preserved for at least 15 years after the completion or discontinuation of/withdrawal from the study or 2 years after the last approval of a marketing application in an International Conference on Harmonization region, whichever is the longer time period.

The Investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of participant health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR, Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 [HIPAA] Privacy Regulation). The Investigator shall ensure that study participants authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the Sponsor.

13.6 Monitoring

The study will be monitored to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.

On-site monitoring visits will be made at appropriate times during the study. Clinical monitors must have direct access to source documentation in order to check the completeness, clarity, and consistency of the data recorded in the eCRFs/CRFs for each subject.

The Investigator will make available to the clinical monitor source documents and medical records necessary to complete eCRFs/CRFs. In addition, the Investigator will work closely with the clinical monitor and, as needed, provide them appropriate evidence that the conduct of the study is being done in accordance with applicable regulations and GCP guidelines.

inVentiv Health Clinical will perform remote monitoring and will also visit the clinical sites every 16 weeks. An experienced medical team will be reviewing the emerging data and will also be available to participating centers to address any clinical questions including

safety-related questions. Both participant level data and aggregated data will be routinely reviewed to ensure no unexpected events are observed.

13.7 Quality Control and Quality Assurance

Weekly registration reports will be generated to monitor participant accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

13.8 Protocol Amendment and Protocol Deviation

13.8.1 Protocol Amendment

Any changes to the protocol will require a formal amendment. This includes substantial changes, as well as those that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no impact on the safety of participants or the conduct of the study. All protocol amendments will be submitted to the IRB/IEC and, as required, to the appropriate Regulatory Authorities.

13.8.2 Protocol Deviations

Should a protocol deviation occur, the Sponsor must be informed. Protocol deviations and/or violations and the reasons they occurred will be included in the clinical study report. It is the investigator's responsibility to report protocol deviations inVentiv Health and the MSKCC research team for submission to the HRPP office in accordance with applicable Regulatory Authority mandates. Prospective deviation requests will not be allowed.

13.9 Ethical Considerations

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the CFR, and in compliance with GCP guidelines.

IRBs/IECs will review and approve this protocol and the ICF. All participants are required to give written informed consent prior to participation in the study.

13.10 Financing and Insurance

Prior to the study commencing, the Sponsor (or its designee) and the Investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement that will be signed by the Investigator (or the institution signatory) and the Sponsor (or its designee).

The Investigator is required to have adequate current insurance to cover claims for its negligence and/or malpractice. The Sponsor, or the manufacturer of the study drug, will provide insurance coverage for the clinical study as required by national regulations.

13.11 Study and Site Closure

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Reasons for terminating the study may include, but are not limited to the following:

- Discontinuation of further stud intervention development
- The incidence or severity of adverse events in this or other studies indicate the potential hazard to participants
- Participant enrollment is unsatisfactory

The Sponsor will notify the Investigator if the Sponsor decides to discontinue the study. Reasons for early closure of a study site by the Sponsor or investigator may include, but are not limited to:

- Poor protocol adherence
- Inaccurate or incomplete data recording
- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- No study activity (ie, all participants have completed the study and all obligations have been fulfilled)

13.12 Publication Policy / Disclosure of Data

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the Investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the Institution and the Sponsor or their designee.

14 REFERENCES

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15 APPENDICES

15.1 Appendix 1: Product Information and Pharmacy Manuals

PRODUCT INFORMATION TABLE

Table Product Description

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
Nivolumab BMS-936558-01 Solution for Injection[a]	100 mg (10 mg/mL)	10 mL vial	5-10 vials per carton/ Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect form light and freezing
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	40 mL vial	4 vials per carton/Open-label	Clear, colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect from light and freezing.

a Nivolumab may be labeled as BMS-936558-01 Solution for Injection

If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab and ipilimumab include laboratory coats and gloves.

Nivolumab and ipilimumab will be given together every 3 weeks for 4 doses.

Nivolumab dose = 1 mg/kg

Ipilimumab dose = 3 mg/kg

When study drugs (ipilimumab or nivolumab) are to be administered on the same day, separate infusion bags and filters must be used for each infusion. It is recommended that nivolumab be administered first. The second infusion will always be ipilimumab and will start approximately 30 minutes after completion of the nivolumab infusion.

BMS-936558 (nivolumab) is to be administered approximately as a 60-minute IV infusion. Ipilimumab should be administered approximately as a 30-minute infusion following. Ipilimumab and nivolumab may be diluted in 0.9% Sodium Chloride Solution or 5% Dextrose solution.

The dosing calculations should be based on body weight, which will be assessed at Screening and Day 1 of each cycle. Dose adjustments are not required unless the participant has a 10% change compared with their initial weight on Cycle 1, Day 1. Drug should be measured according to institutional guidelines.

Nivolumab (BMS-936558) Pharmacy Reference Material
As this is provided for guidance only, please see Investigator's Brochure (IB) for additional information regarding preparation and administration
Nivolumab has a concentration of 10 mg/mL and is provided in a 10 mL vial. Ten or 5 vials are provided in a carton.

Storage Conditions & Handling:

- Store at 2-8°C (36-46°F), protect from light, freezing, and shaking.
- If any temperature excursions are encountered during storage, please report these to BMS for assessment via the Temperature Excursion Response Form.
- As with all injectable drugs, care should be taken when handling and preparing nivolumab. Whenever possible, nivolumab should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of IV agents applying aseptic technique.
- Partially used vials should be disposed at the site following procedures for the disposal of anticancer drugs.

After final drug reconciliation, unused nivolumab vials should be disposed at the site following procedures for the disposal of anticancer drugs. For further information, please either discuss with your BMS CSR&O protocol manager or refer to your site IP Destruction policies and procedures

Use Time/Stability: Please refer to the appropriate section of the current IB or Addendum. Due to parameters surrounding the use time of nivolumab and ipilimumab, the time of preparation should be noted in the Pharmacy Source documents [accountability logs] or in study files as required for investigator sponsored research [FDA and GCP].

The administration of BMS-936558-01 injection prepared for dosing nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored up to 20 hours in a refrigerator at under refrigeration conditions (2°-8°C (36°-46°F) and used within 24 hours, and a maximum of 8 hours of the total 24 hours can be at room temperature (20°-25°C, 68°-77°F) and under room light. The maximum 4-hour period under room temperature and room light conditions for undiluted and diluted solutions of BMS-936558-01 injection in the IV bag includes the product administration period.

Preparation and Administration:

1. Visually inspect the drug product solution for particulate matter and discoloration prior to administration. Discard if solution is cloudy, if there is pronounced discoloration (solution may have a pale-yellow color), or if there is foreign particulate matter other than a few translucent-to-white, amorphous particles. *Note: Mix by gently inverting several times. Do not shake.*
2. Aseptically withdraw the required volume of nivolumab solution into a syringe and dispense into an IV bag. If multiple vials are needed for a participant, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall. **Do not**

enter into each vial more than once. **Do not** administer study drug as an IV push or bolus injection

3. Add the appropriate volume of 0.9% Sodium Chloride Injection solution or 5% Dextrose Injection solution. It is acceptable to add nivolumab solution from the vials into an appropriate pre-filled bag of diluent.
4. **Note: Nivolumab infusion concentration must be at or above the minimum allowable concentration of 0.35 mg/mL [IBV13 Addendum Section 3.2.2]**
5. Note: It is not recommended that so-called "channel" or tube systems are used to transport prepared infusions of nivolumab.
6. Attach the IV bag containing the nivolumab solution to the infusion set and filter.
7. At the end of the infusion period, flush the line with a sufficient quantity of approved diluents.

Ipilimumab Pharmacy Reference Material

Ipilimumab vials (40 mL) are shipped in quantities of four.

Ipilimumab (BMS-734016) Injection (5 mg/ml) must be stored refrigerated (2-8°C, 36-46°F) with protection from light and from freezing. Ipilimumab may be stored in IV infusion bags (PVC, non-PVC/non-DEHP) or glass infusion containers for up to 24 hours at room temperature (20-25°C, 68-77°F) or refrigerated (2-8°C, 36-46°F). This would include any time in transit and the total time for infusion. Drug must be completely delivered within 24 hours of preparation.

Storage Conditions & Handling:

Ipilimumab injection may be stored undiluted, 200 mg/vial (5 mg/mL), or following dilution to concentrations between 1 mg/mL and 4 mg/mL in 0.9% Sodium Chloride Injection (USP), or 5% Dextrose Injection (USP) in PVC, non-PVC/ or glass containers for up to 24 hours in the refrigerator (2°C to 8°C) or at room temperature/room light. For longer storage, ipilimumab should be kept refrigerated (2°C to 8°C) with protection from light.

Ipilimumab injection must not be frozen.

Partially used vials or empty vials of Ipilimumab Injection should be discarded at the site according to appropriate drug disposal procedures.

Preparation and Administration

As this is provided for guidance only, please see IB for additional information regarding preparation and administration.

1. As ipilimumab is stored long term at refrigerated temperatures (2-8ºC) and protected from light, allow the appropriate number of vials of ipilimumab to stand at room temperature for approximately five minutes.
2. Ensure that the ipilimumab solution is clear colorless, essentially free from particulate matter on visual inspection. If multiple vials are needed for a participant, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as

dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall, etc.

3. Aseptically transfer the required volume of ipilimumab solution into a syringe. [Note: A sufficient excess of ipilimumab is incorporated into each vial to account for withdrawal losses].
4. Do not draw into each vial more than once. Discard partially used vials or empty vials.
5. Ipilimumab solution should be added to an appropriate size infusion container to accommodate the calculated final volume.
   Dose calculations should be based on body weight, which will be assessed at Screening and Day 1 of each cycle. Dose adjustments are not required unless the participant has a 10% change compared with their initial weight on Cycle 1, Day 1. Drug should be measured according to institutional guidelines.
   Mix by GENTLY inverting several times. DO NOT shake.
   Ipilimumab injection may be diluted in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP.
6. Visually inspect the final solution. If the initial diluted solution or final solution for infusion is not clear or contents appear to contain precipitate, the solution should be discarded.
7. Immediately after the infusion is complete, flush with an adequate amount of 0.9% Sodium Chloride injection (USP) or 5% Dextrose injection (USP) to completely flush the residual fluid (dead space) in your administration set (approximately 30-50 mL); this will ensure that all active drug is delivered to the study participant.
8. Safely discard any unused portion of the infusion solution. Do not store for reuse.

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

15.2 Appendix 2: Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab and ipilimumab are considered immuno-oncology agents in this protocol. Management algorithms have been developed to assist investigators in assessing and managing the following groups of AEs: Gastrointestinal, Renal, Pulmonary, Hepatic, Endocrinopathies, Skin, and Neurological.

Early recognition and intervention are recommended according to the management algorithms; and in addition include ophthalmologic evaluations for any visual symptoms in order to evaluate for nivolumab or ipilimumab related uveitis.

The recommendations are to follow the algorithms in the nivolumab IB for immune related events; while the ipilimumab IB contains similar algorithms, the algorithms in the nivolumab brochure have been aligned to accommodate combinations as well as nivolumab monotherapy.

Therefore, the algorithms recommended for utilization are attached for reference.
For participants expected who require more than 4 weeks of corticosteroids or other immunosuppressants to manage an AE, consider the following recommendations.

- Antimicrobial/antifungal prophylaxis per institutional guidelines to prevent opportunistic infections such as *Pneumocystis jiroveci* and fungal infections.
- Early consultation with an infectious disease specialist should be considered. Depending on the presentation, consultation with a pulmonologist for bronchoscopy or a gastroenterologist for endoscopy may also be appropriate.
- In participants who develop recurrent AEs in the setting of ongoing or prior immunosuppressant use, an opportunistic infection should be considered in the differential diagnosis.

Additional details on the safety of nivolumab and ipilimumab, including results from clinical studies, are available in the IB.

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol	Continue to monitor the patient. If worsens: • Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	If improves to baseline: •Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Renal Adverse Event Management Algorithm

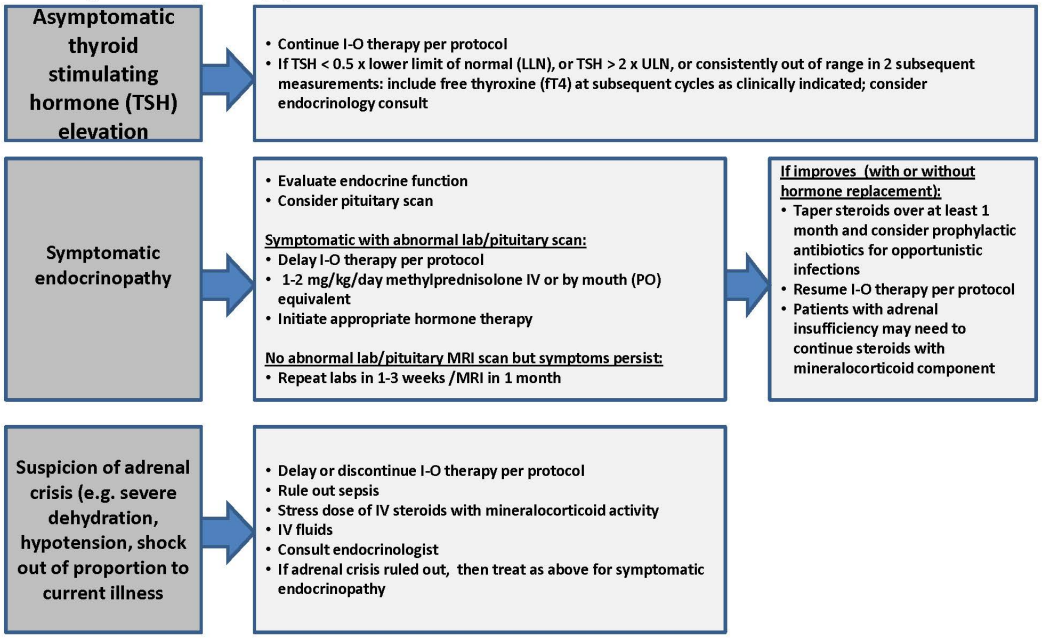
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy

Grade of Creatinine Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 Creatinine > upper limit of normal (ULN) and > than baseline but ≤ 1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	If returns to baseline: •Resume routine creatinine monitoring per protocol If worsens: •Treat as Grade 2 or 3/4
Grade 2-3 Creatinine > 1.5x baseline to ≤ 6x ULN	• Delay I-O therapy per protocol • Monitor creatinine every 2-3 days • 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy	If returns to Grade 1: •Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol If elevations persist > 7 days or worsen: •Treat as Grade 4
Grade 4 Creatinine > 6x ULN	• Discontinue I-O therapy per protocol • Monitor creatinine daily • 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrologist • Consider renal biopsy	If returns to Grade 1 : Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Endocrinopathy Management Algorithm

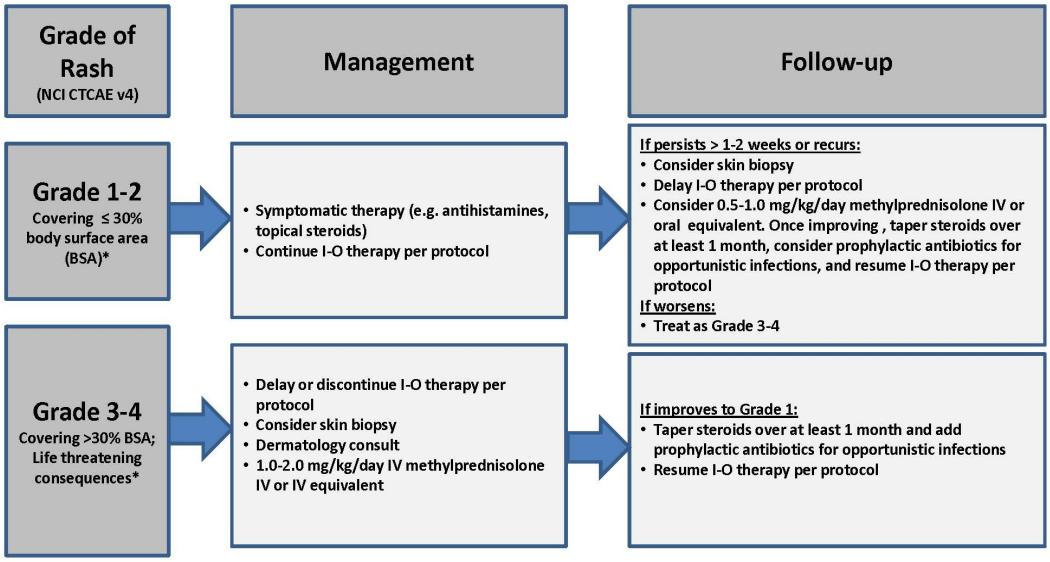
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Skin Adverse Event Management Algorithm

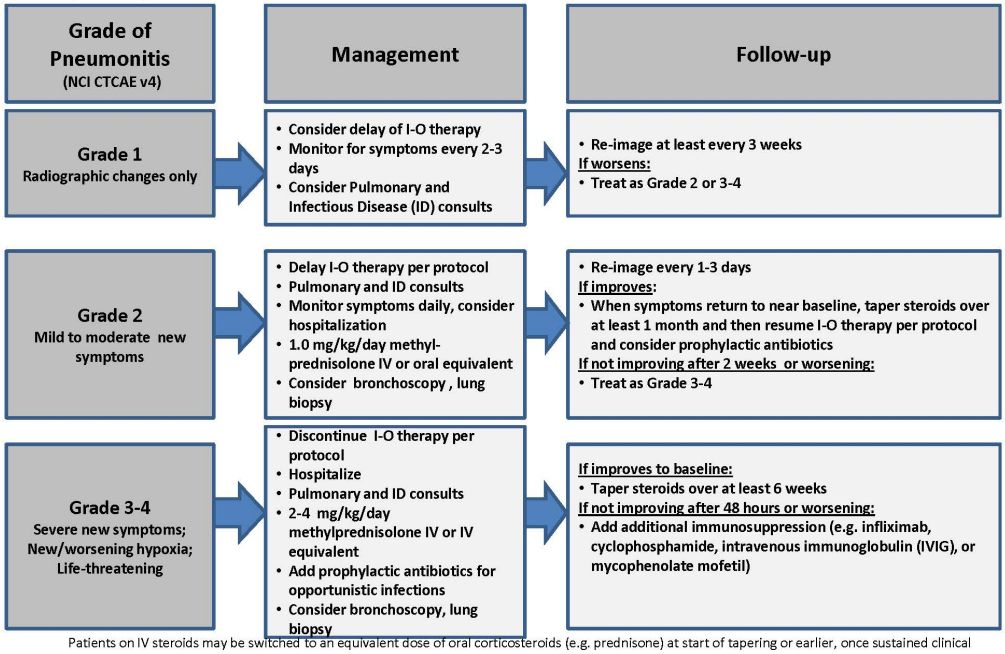
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.

Pulmonary Adverse Event Management Algorithm

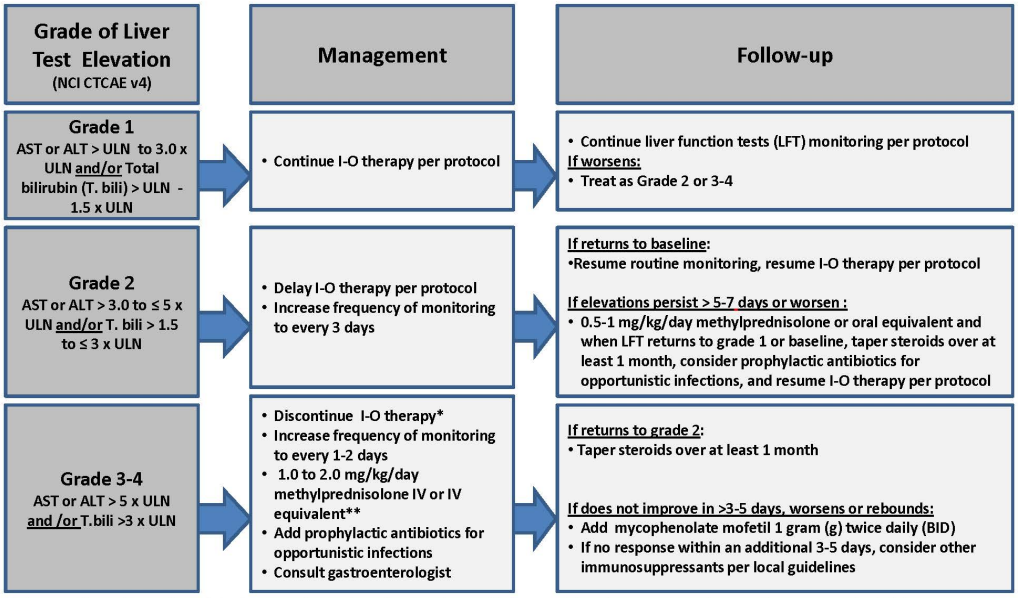
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Hepatic Adverse Event Management Algorithm

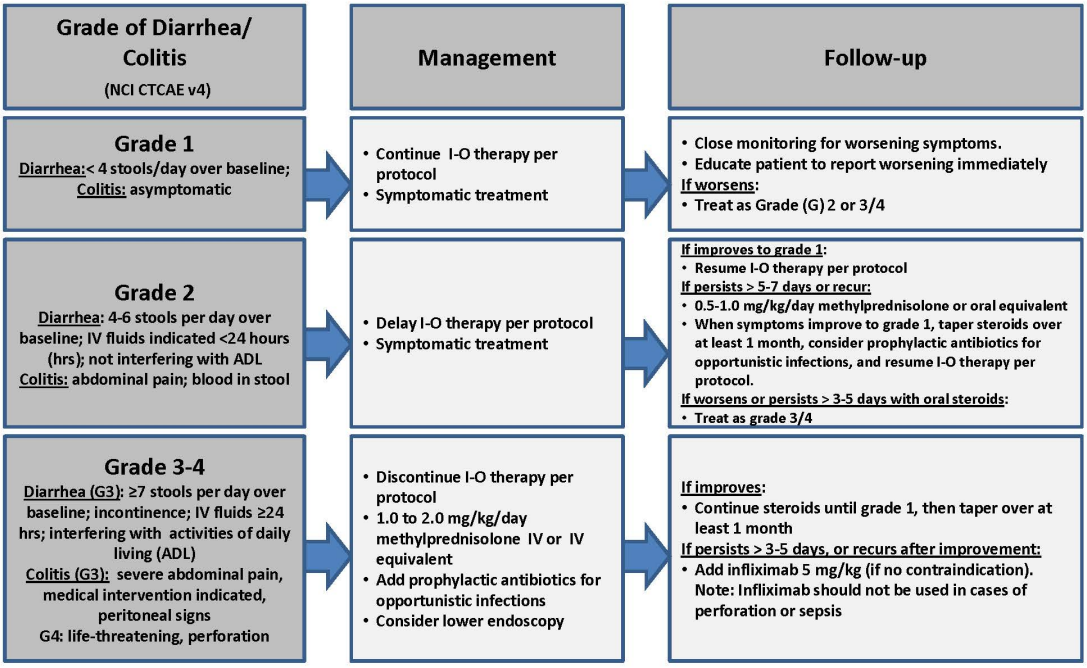
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN and T.bili ≤ 5 x ULN.**
**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

15.3 Appendix 3: Laboratory Procedures

A variety of factors that could potentially predict clinical response to ipilimumab alone or in combination with nivolumab will be investigated in peripheral blood and in tumor specimens taken both pre- and post-treatment. All samples collected and banked may also be used for future exploratory analyses.

All sites will send samples, collected in the kits that are provided by Parker Institute for Cancer Immunotherapy, to a centralized biorepository location. The samples will be shipped from the biorepository to a centralized testing location for analysis. Sites will not be required to do any exploratory testing unless they have been identified as a testing site and the budgeting for that will be established separately.

Tumor tissue specimens

Pre- and on- treatment tumor specimens will be obtained on all eligible participants. Tumor specimens collected may include (1) 4 core biopsy specimens or (2) an excision biopsy or (3) a specimen from surgical resection of a tumor. In the case of the core biopsy specimens, 3 core biopsies will be snap frozen and 1 biopsy will be formalin fixed and preserved in paraffin embedded blocks (FFPE). In the case of excisional or surgical specimens, approximately ½ of the specimen will be snap frozen and the other ½ will be formalin fixed and paraffin embedded.

Analysis of immune infiltrate
Analysis of immune infiltrate will be performed using IHC and/or flow cytometry. Populations of cells analyzed may include, but will not be limited to, CD4, CD8, T_{reg} populations, B cells, MDSC, monocytes, dendritic cells and expression of biologically relevant/phenotypic markers thereof. Standard established institutional protocols will be applied. Changes to these methods may be adapted depending upon the most recent, generally accepted protocols.

PD-L1 Expression

PD-L1 expression will be assessed on both pre-treatment and on-treatment tumor biopsies in the form of formalin fixed paraffin embedded block or unstained slides. PD-L1 stained tissue sections will be assessed by a pathologist and membranous PD-L1 expression scored in tumor and immune cells. PD-L1 expression will be graded as positive for negative, according to the most up to date standards for the assay in use. Changes to these methods may be adapted depending upon the most recent, generally accepted protocols.

Gene Expression Profiling:
Gene expression profiling on tumor samples will be run using different methodologies. Genes of interest include but are not limited to cell surface makers such as CD4 and CD8, checkpoint molecules such as LAG3 and genes relevant to the interferon pathway. Standard established institutional protocols will be applied. Changes to these methods may be adapted depending upon the most recent, generally accepted protocol.

RNA and DNA Preparation
Core biopsies will be used to extract DNA or RNA. Whole blood samples will be collected in a lavender top tube for purification of RNA/DNA. Standard established institutional protocols will be applied. Changes to the methods for RNA and DNA preparation may be adapted depending upon the most recent, generally accepted protocols.

Exome sequencing of Tumor DNA and matched Normal DNA from Blood
Exome sequencing will be carried out on Illumina Hiseq 2100 to a mean target coverage of 150X using 500 ng of genomic DNA from frozen tissue as input. Changes to the methods for exome sequencing may be adapted depending upon the most recent, generally accepted protocols.

Transcriptome Sequencing of Tumor RNA
RNA-Seq analysis will be performed on samples with sufficient material. Sequencing libraries will be prepared from total RNA with the Illumina TruSeq mRNA library kit (v2) and then sequenced on the HiSeq 2500 with 2x50bp paired reads, yielding 47-60M reads per sample. The RNA reads will be aligned using the STAR aligner after which Cufflinks was used for gene quantification (FPKM). Changes to these methods may be adapted depending on the most recent, generally accepted protocols.

Somatic Mutation Identification and Verification

Raw sequencing data will be mapped to the human reference genome. Alignment, base-quality score recalibration, duplicate-read removal, and exclusion of germline variants will be performed using the Genome Analysis Toolkit (GATK). Known single nucleotide polymorphisms will be eliminated. Mutations will be annotated using SnpEffect, called with Somatic Sniper, VarScan, Strelka and MuTect then filtered and manually reviewed using IGV. Insertion and deletions (indels) will be called using Strelka.

Changes to these methods may be adapted depending on the most recent, generally accepted protocols.

Neoantigen Prediction

For each somatic SNV appearing in expressed genes, reference and mutated peptide sequences are generated. Each variant is linked to its corresponding coding DNA sequence (CDS) from Ensembl based on its B37 coordinates. The CDS is re-translated with the mutated DNA residue producing the mutated peptide product. NetMHCCons v1.1 generates a predicted binding affinity for all 8 to 11mers containing the mutated amino acid and all peptides with an IC50 score below 500nM are considered predicted neoepitopes. Changes to these methods may be adapted depending upon the most recent, generally accepted protocols.

Exploratory Serum and Plasma Biomarkers

Blood samples for exploratory serum and plasma biomarker analyses will be drawn at the time points indicated in Table 3. Changes to these methods may be adapted depending upon the most recent, generally accepted protocols.

Peripheral blood analysis

Analysis of peripheral blood populations will be performed using flow cytometry and/or computational approaches (deconvolution) based upon RNA sequencing data analysis. Populations of cells analyzed may include, but will not be limited to, CD4, CD8, T_{reg} populations, B cells, MDSC, monocytes, dendritic cells and expression of biologically relevant/phenotypic markers thereof. Standard established institutional protocols will be applied. Changes to these methods may be adapted depending upon the most recent, generally accepted protocols.

15.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories **are not considered WOCBP**

1. Premenarchal
2. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

    Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

Male Participants

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

In addition, male participants must refrain from donating sperm for the duration of the study and for 7 months after the last dose of study intervention.

Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame and for 7 months after the last dose of study intervention.

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table below.

Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent[a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

NOTES:

a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period and for at least 5 months after the last dose of study intervention.

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test within 24 hours of first dose.
- Additional pregnancy testing should be performed every 3 cycles during the treatment period.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Collection of Pregnancy Information

Male Participants with Partners who Become Pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who Become Pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the Sponsor as described in Section 11.1.3. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.