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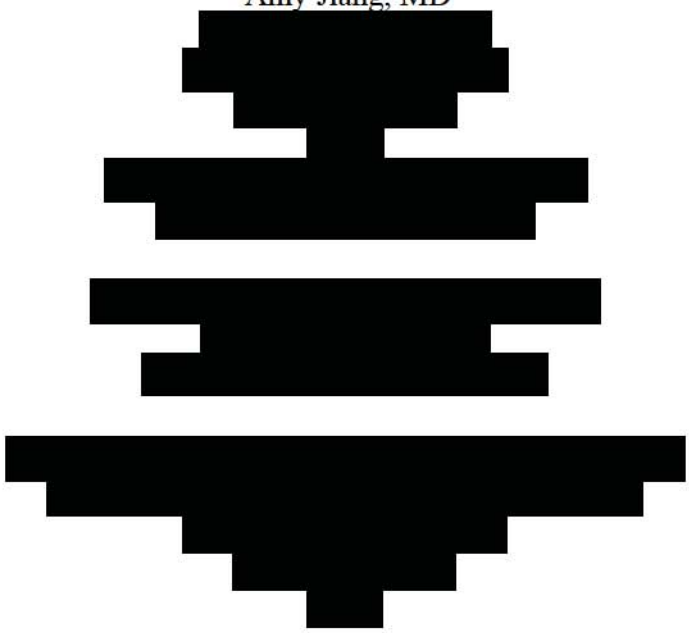
Clinical Protocol CA184248

A Randomized, Open-Label, Two-arm, Comparative Study in Chinese Subjects with Chemotherapy Naïve Stage IV Melanoma Receiving Ipilimumab (3 mg/kg) vs. Dacarbazine.

Revised Protocol Number: 04

Study Director & Medical Monitor

Amy Jiang, MD



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Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 04	28-Jun-2019	Revised to incorporate changes for the Re-Induction phase of the protocol.
Revised Protocol 03	20-Dec-2018	Incorporates Amendment 03 and Administrative Letter 04
Amendment 03	20-Dec-2018	Modify the primary endpoint from overall survival (OS) to the 2-year OS rate.
Administrative Letter 04	20-Nov-2018	Updated Study Director/Medical Monitor information
Administrative Letter 03	05-Feb-2018	Updated Study Director/Medical Monitor information
Administrative Letter 02	08-Feb-2017	Updated Study Director/Medical Monitor information
Administrative Letter 01	11-Aug-2016	Updated Study Director/Medical Monitor information
Revised Protocol 02	23-Dec-2015	Incorporates Amendment(s) 02
Amendment 02	23-Dec-2015	The purpose of this amendment is to remove the use of a Data Monitoring Committee (DMC) since: 1. This is an open label study; 2. This is a single country study (China) and not a MRCT (Multi Regional Clinical Trial) and therefore an independent DMC is not required as per the Chinese regulation. In addition, this amendment provides further clarification with regards to: 1. The infusion pump used for the administration of ipilimumab 2. The T&E schedule (Endocrine assessments and collection of PK/ADA)
Revised Protocol 01	08-Jul-2015	Incorporates Amendment(s) 01
Amendment 01	08-Jul-2015	- Update the dose of DTIC per China label requirement. - Other changes per program level standards and model document
Original Protocol	11-Mar-2013	Not applicable

OVERALL RATIONALE FOR REVISED PROTOCOL 04:

The purpose of this amendment is to monitor patients who are in follow-up after having received ipilimumab during the Induction phase and have the potential to receive ipilimumab upon progression. One course of ipilimumab may be provided to these patients upon documentation of progression.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis	Replaced previous content with Re-Induction phase information.	Synopsis was updated to reflect the changes in the body of the protocol as summarized below.
Section 1: Introduction and Study Rationale		
Section 1.2, Research Hypothesis; and Synopsis, under heading for Research Hypothesis	Updated text that no formal research hypothesis will be tested in the Re-Induction phase.	Updated for clarity.
Section 1.3.1, Primary Objectives; and Synopsis, under heading for Primary Objective	Updated the primary objective.	This amendment is for one site as the site has 2 patients that may enter Re-induction phase upon progression.
Section 1.3.2, Secondary Objectives; and Synopsis, under heading for Secondary Objectives	Secondary objectives were changed to indicate that safety data will be collected and reported according to health authority and BMS regulations.	No further data will be collected in the database.
Section 1.3.3, Exploratory Objectives	Exploratory objectives are no longer applicable.	No exploratory objectives.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3: Investigational Plan		
Section 3.1, Study Design and Duration; Screening Phase; Induction Phase; Section 3.2, Post Study Access to Therapy; Section 3.6.1, Withdrawal of Consent	Replaced previous content with Re-Induction phase information. Screening and Induction phases have been completed.	Updated for Re-Induction phase.
Figure 3.1-1, Re-Induction phase Design Schematic; and Synopsis under Study Design heading	Renamed figure and replaced Study Design Schematic with Re-Induction Phase Design Schematic.	Updated for clarity.
Section 3.1, Study Design and Duration; Re-Induction Phase (only for subjects randomized to ipilimumab)	Added bullet item: "Re-Induction criteria must be reviewed with the BMS Medical Monitor before the Drug Order form is completed and submitted;" Revised bullets regarding the number of doses of ipilimumab; treatment assessments; and discontinuation.	Updated for clarity.
Toxicity/ Progression Follow-up Phase; Overall Survival Follow up Phase	Deleted content regarding the Induction phase, Toxicity/ Progression Follow-up Phase, and Overall Survival Follow-Up Phase.	

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.3.1, Inclusion Criteria Criterion 3, Age and Reproductive Status	Added a sentence indicating that Re-Induction phase is outlined in Section 3.3.2.1. Removed information on WOCBP subjects that were randomized to DTIC.	Updated for clarity
Section 3.3.2, Exclusion Criteria	Added a sentence indicating that exclusion criteria for Re-Induction phase are outlined in Section 3.3.2.1.	Updated for clarity.
Section 3.6, Post Treatment Study Follow up Section 3.6.2, Lost to Follow-Up	Previous text was deleted, and this section was changed to 'not applicable'.	Not applicable.
Section 4, Treatments		
Table 4.1-1, Product Description - Ipilimumab (Induction and Re-Induction Phases) Synopsis under Investigational Products heading	DTIC information was deleted and subsequent sections were updated. Added sentence stating: "In this protocol amendment, investigational product is: Ipilimumab 5 mg/mL solution."	DTIC is not applicable in Re-Induction phase.
Section 4.2, Method of Assigning Subject Identification	Previous text was deleted, and a sentence was added stating: "Enrolled subjects have already been assigned a unique identification number."	Updated for clarity.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 4.3.2, DTIC; Sections 4.3.4, Dose Modification Criteria - DTIC through Section 4.3.4.3, Permanent Discontinuation of DTIC	Sections regarding DTIC were deleted.	Not applicable in Re-Induction phase.
Section 5: Study Assessments and Procedures		
Section 5.1, Flow Chart/Time and Events Schedule	Tables in this section were revised (or deleted as applicable) for Re-Induction phase.	Updated for Re-Induction phase.
Table 5.1-3, Procedural Outline - Re-Induction Phase (CA184248)	This table was renumbered to Table 5.1-1. and updated for Re-Induction phase.	Updated for clarity.
Section 5.1.1, Retesting During Screening or Lead-in Period Section 5.4.8.1, Missing Assessments and Not Evaluable Designation Section 5.5, Pharmacokinetic Assessments	Previous text was deleted and section was changed to "Not applicable."	Screening and Lead-in periods are completed. No additional data will be collected, except Safety.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 5.2, Study Materials	Updated for Re-Induction phase including: addition of Pregnancy Surveillance Form, Drug Order form, and BMS SAE reporting form	Updated for clarity.
Sections 5.3.1, Imaging Assessment for the Study through Section 5.3.3, Vital Signs	Revised assessments to be evaluated per standard of care.	The purpose of this amendment is to monitor patients who are in follow-up after having received ipilimumab during the Induction phase and have the potential to receive ipilimumab upon progression. No data will be collected.
Section 5.3.4, ECG	Changed to "Required as clinically indicated."	Screening and Lead-in periods are completed. No additional data will be collected, except Safety.
Section 5.3.6, ECOG Performance Status	Changed to "Eastern Cooperative Oncology Group (ECOG) Performance Status will be evaluated as outlined in Section 5.1."	Screening and Lead-in periods are completed. No additional data will be collected, except Safety.
Sections 5.4.1, Primary Efficacy Assessment through Sections 5.4.2.1, Radiographic Assessments; Section 5.4.3, Assessment on Overall Tumor Burden; Section 5.4.4.1, Measurement of Lesions; Section 5.4.5.1, Target Lesions; Section 5.4.5.3, Non-target Lesions; Section 5.4.8,	Section revised for Re-Induction phase.	The purpose of this amendment is to monitor patients who are in follow-up after having received ipilimumab during the Induction phase and have the potential to receive ipilimumab upon progression. No data will be collected.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Response Criteria (RECIST 1.1)		
Section 5.7, Outcomes Research Assessments	Revised to indicate that Outcome Research Assessment will not be collected.	No exploratory objectives.
Section 5.7.3, Health Related Resource Utilization	Revised to indicate that Health Related Resource Utilization data will not be collected.	Updated for clarity.
Section 6: Adverse Events		
Section 6.1.1, Serious Adverse Event Collection and Reporting	Updated information on SAE reporting. The investigator should report any SAEs and pregnancies via paper forms to worldwide.safety@bms.com or via facsimile 609-818-3804, or telephone +1-248-844-7390	Adverse Events will no longer be collected via CRF; however, sites are still required to report the AEs.
Section 6.2.1, Nonserious Adverse Event Collection and Reporting	Removed text regarding nonserious AE information at initiation of study drug. Added requirement to record any nonserious AE not already listed in IB.	As Adverse Events will no longer be collected via CRF, updated for clarity.
Section 8: Statistical Considerations		
Section 8.1, Sample Size Determination	Updated sample size to 2 patients eligible for Re-Induction.	Updated for clarity.
Section 8.2, Populations for Analyses	Revised to: No analysis will be conducted.	Updated for clarity.
Section 8.3, Endpoints	Revised to not applicable.	No formal research hypothesis will be tested in the Re-Induction phase.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 8.3.4, Safety	Section renumbered to Section 8.3.1 and revised for Re-Induction phase.	Updated for clarity.
Previous sections numbered: Section 8.3.4.1, Pharmacokinetics of Ipilimumab; through Section 8.3.4.4, Health Related Resource Utilization	Sections deleted.	Updated for clarity.
Previous section numbered: Section 8.4.1, Demographics and Baseline Characteristics	Section deleted.	Data already collected.
Previous section numbered: Section 8.4.2, Efficacy Analyses	Section renumbered to Section 8.4.1 and text was changed to "Not applicable."	No formal research hypothesis will be tested in the Re-Induction phase.
Previous section numbered: Section 8.4.3, Safety Analyses	Section renumbered to Section 8.4.2 and text was changed to "No safety analysis will be conducted."	Updated for clarity.
Previous section numbered: Section 8.4.4, Pharmacokinetic Analyses	Section renumbered to Section 8.4.3 and text was changed to "Not applicable."	Updated for clarity.
Previous section numbered: Section 8.4.6, Outcomes Research Analyses	Section renumbered to Section 8.4.5 and text was changed to "Not applicable."	Updated for clarity.

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Previous section numbered: Section 8.4.7, Other Analyses	Section renumbered to Section 8.4.6 and text was changed to "Not applicable."	Updated for clarity.
Section 9: Study Management		
Section 9.2.2, Study Drug Records	BMS will no longer provide forms to facilitate inventory control for sites that do not have a system that meets requirements.	Updated for clarity.
Section 9.2.3, Case Report Forms	Only requirements are to prepare and maintain accurate case histories, recording all observations and data pertinent to study. Also, privacy and confidentiality must be protected.	Updated for clarity.
Global Changes	References were updated. Minor typographical changes.	Global updates.

SYNOPSIS

Clinical Protocol CA184248

Protocol Title: A Randomized, Open-Label, Two-arm, Comparative Study in Chinese Subjects with Chemotherapy Naïve Stage IV Melanoma Receiving Ipilimumab (3 mg/kg) vs. Dacarbazine.

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): ipilimumab 3 mg/kg to be administered via intravenous infusion over 90 minutes at Weeks 1, 4, 7 and 10, for a total of four doses in Induction (and Re-Induction for those randomized to the ipilimumab arm who qualify) and DTIC 250 mg/m^2 - Day 1 - 5, to be administered via intravenous infusion at Weeks 1, 4, 7, 10, 13, 16, 19, and 22.

In this protocol amendment, investigational product is: Ipilimumab 5 mg/mL solution.

Study Phase: II

Research Hypothesis (for the Induction phase): Among chemotherapy naive Chinese subjects with Stage IV melanoma, the 2-year OS (OS) rate in Chinese subjects who have been randomized to ipilimumab 3 mg/kg will be superior to that in Chinese subjects who have been randomized to DTIC 250 mg/m^2 - Day 1 - 5. Database lock date was 03Jun2019.

No formal research hypothesis will be tested in the Re-Induction phase.

Objectives:

Primary Objective:

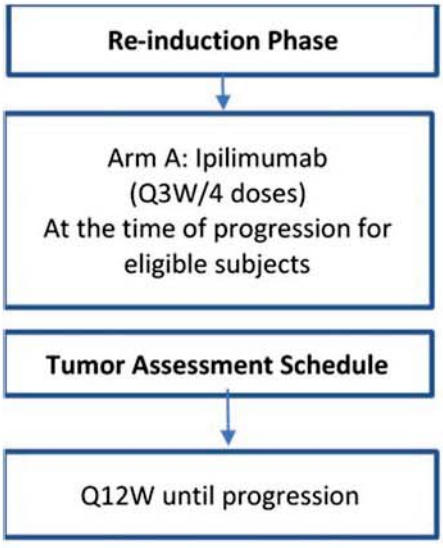
The purpose of this site specific amendment is to monitor patients who are in follow-up after having received ipilimumab during the Induction phase and have the potential to receive ipilimumab upon progression. One course of ipilimumab may be provided to these patients upon documentation of progression. No formal research hypothesis will be tested.

Secondary Objectives:

Safety data will be collected and reported according to health authority regulations and BMS regulations.

Study Design: This is an open-label study to provide ipilimumab to patients eligible for Re-Induction.

Re-Induction Phase Design Schematic



Study Population: Chinese subjects ≥ 18 years of age with histologic diagnosis of chemotherapy naive measurable and/or non-measurable Stage IV melanoma and Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Subjects must not have primary ocular or mucosal melanoma or brain metastases. Prior therapy with chemotherapy agents (eg, DTIC, Temozolomide), experimental vaccines, immunosuppressive agents, other investigational anti-cancer chemotherapies, or chronic use of systemic corticosteroids is not permitted. Prior adjuvant therapy is not exclusionary. Prior TKI for BRAF and cKIT mutant melanoma is permitted.

Subjects who were randomized to the ipilimumab arm may have been eligible to enter the Re-Induction phase if they met the following criteria within 28 days of Re-Induction: Initial objective response (PR or CR) or stable disease of ≥ 3 months was achieved after the Induction phase and subsequent documented progression, did not experience any AEs that required permanent discontinuation of ipilimumab, or experienced a dose delay > 21 days due to toxicity, did not discontinue ipilimumab for any reason, and met the Re-Induction physical and laboratory test findings.

Study Assessments:

Subject survival was ascertained via regular study visits to support the primary endpoint of 2-year OS rate. During the Re-Induction phase, tumor assessments will be performed every 12 weeks or per standard of care until documented PD or withdrawal of consent.

Statistical Considerations:

Sample Size: There are two patients eligible for Re-Induction.

Endpoints: Not applicable.

Analyses: No analysis will be conducted. Safety data need to be collected until 90 days after the last dose of study medication is received.

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[redacted]

1.2 Research Hypothesis

No formal research hypothesis will be tested in the Re-Induction phase.

For the Induction phase, the hypothesis was — among chemotherapy naive Chinese subjects with Stage IV melanoma, the 2-year OS rate in Chinese subjects who have been randomized to ipilimumab 3 mg/kg will be superior to that in Chinese subjects who have been randomized to DTIC (250 mg/m^2, Day 1 - 5). Database lock date was 03Jun2019.

1.3 Objectives(s)

1.3.1 Primary Objectives

The purpose of this site specific amendment is to monitor patients who are in follow-up after having received ipilimumab during the Induction phase and have the potential to receive ipilimumab upon progression. One course of ipilimumab may be provided to these patients upon documentation of progression. No formal research hypothesis will be tested.

1.3.2 Secondary Objectives

Safety data will be collected and reported according to health authority regulations and BMS regulations.

1.3.3 Exploratory Objectives

Not applicable.

1.4 Product Development Background

Ipilimumab is a fully human monoclonal immunoglobulin (IgG1κ) specific for human cytotoxic T lymphocyte antigen, which is expressed on a subset of activated T cells. The proposed mechanism of action for ipilimumab is T cell potentiation through interference of the interaction of CTLA-4 with B7 molecules on antigen presenting cells with subsequent blockade of the inhibitory function of CTLA-4. Blockade of CTLA-4 (CD152) is a new approach of the treatment of human cancers that offers an immune-mediated alternative to cancer treatment. CTLA-4 is an activation-induced T-cell surface molecule. CTLA-4 mediated signals are inhibitory and turn off T-cell dependant immune response. Disrupting CTLA-4 interaction with its ligand B7-1 (CD80) and B7-2 (CD86), which are expressed on APCs, strengthens the immune responses and augments T-cell activation and proliferation (Figure 1.1.2-1).

The survival benefit and tolerability of ipilimumab as a single agent at a dose of 3 mg/kg administered every 3 weeks for 4 doses has been established in MDX010-020 in previously treated population, which led to the approval of ipilimumab by several countries including the United States Food and Drug Administration (FDA), for the treatment of patients with unresectable or metastatic melanoma and in the European Medicines Agency (EMA) for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy. The survival benefit of ipilimumab was subsequently demonstrated in a second Phase 3 study (CA184024) in previously untreated patients with advanced melanoma. However, no Chinese melanoma subjects were enrolled into these two studies.

1.4.1 Assessment of Immune-Mediated Adverse Reactions

The safety profile of ipilimumab has historically been described by irAEs, which are defined as 1) AEs that are related to ipilimumab per investigator and 2) are consistent with an inflammatory process. Recently, BMS conducted an independent, retrospective adjudication of AEs from two randomized Phase 3 trials (MDX010-20 and CA184024). Adjudication of AEs was limited to the common target organs of ipilimumab toxicity (eg, enterocolitis, hepatitis, dermatitis, endocrinopathy) or other less common AEs that may be immune-mediated (eg, neuropathy) and was conducted in a blinded fashion to investigator attribution (eg, irAE). The AEs were adjudicated as being immune mediated or not immune-mediated based on case definitions for ipilimumab-related AEs developed from 1) guidance for evaluation of AEs of interest provided to investigators and 2) review of irAE outcomes and treatments in the Phase 2 and 3 program.

Classification of a potential AE as an immune-mediated adverse reaction (imAR) using these case definitions (provided in the Investigator Brochure) was based on first excluding as imAR based on

1) alternative, non-immune-mediated etiology (eg, tumor progression, infection, concomitant medication/radiation), or

2) unlikely to be immune mediated from ipilimumab based on the behavior of the AE (eg, rapidly resolves without need for immunosuppression).

AEs that could not be excluded as above were then evaluated as "**possibly**" (eg, AE persists > 1 week, previous imAR in same organ) or "**definitely**" (eg, biopsy proven inflammation) imARs. Occasionally, AEs were classified as "**unknown**" due to insufficient information. For summary purposes, AEs were grouped as: not-imAR (excluded as imAR) or an imAR (unknown, definitely, possibly).

As summarized in Table 1.4.1-1, imAR adjudication in MDX010-20 was specific and sensitive for detection of immune mediated AEs since the control arm had a very low rate of 'imARs'. Henceforth, imAR adjudication will be performed by the investigator and not the Sponsor.

The original adjudication and testing of imAR adjudication by Sponsor for MDX010-20 and CA184024 was conducted in a blinded fashion to investigator attribution. Adjudication of an AE as an imAR will generally parallel classification as "related to study drug" since the same evidence is usually used for both. However, in theory, an AE may potentially be classified as "drug related but not an imAR" (eg, related to concomitant chemotherapy where applicable but not immune mediated per imAR criteria). Key differences between a "drug related" AE versus an imAR include:

- imARs require documentation of reason for exclusion or inclusion, while "drug related" AEs do not require documentation and are assigned based on clinical suspicion.
- imARs are determined retrospectively since they require knowledge of AE outcome. imAR case definitions should not be used as guidance for AE management.

Table 1.4.1-1: MDX010-20 Immune-mediated Adverse Reactions (imARs) Grouped by Organ System

Treatment Arm	Number of patients (%)		
	Ipilimumab 3 mg/kg N = 131	Ipilimumab 3 mg/kg + gp100 N = 380	gp100 N = 132
All Types			
Grade 2	34 (26.0)	58 (15.3)	11 (8.3)
Grade 3	16 (12.2)	40 (10.5)	1 (0.8)
Grade 4	2 (1.5)	2 (0.5)	0
Grade 5	1 (0.8)	5 (1.3)	0
Severe (≥ Grade 3)	19 (14.5)	47 (12.4)	1 (0.8)
Enterocolitis			
Grade 2	7 (5.3)	21 (5.5)	1 (0.8)
Severe (≥ Grade 3)	9 (6.9)	25 (6.6)	0
Hepatotoxicity			
Grade 2	8 (5.3)	6 (1.6)	3 (2.3)
Severe (≥ Grade 3)	1 (0.8)	7 (1.8)	0
Dermatitis			
Grade 2	25 (19.1)	38 (10.0)	4 (3.0)
Severe (≥ Grade 3)	3 (2.3)	10 (2.6)	0
Neuropathy			
Grade 2	1 (0.8)	3 (0.8)	2 (1.5)
Severe (≥ Grade 3)	1 (0.8)	1 (0.3)	1 (0.8)
Endocrinopathy			
Grade 2	6 (4.6)	6 (1.6)	1 (0.8)
Severe (≥ Grade 3)	5 (3.8)	4 (1.1)	0
Other			
Grade 2	3 (2.3)	2 (0.5)	2 (1.5)
Severe (≥ Grade 3)	1 (0.8)	3 (0.8)	0

1.5 Overall Risk/Benefit Assessment

Ipilimumab has been evaluated in a number of indications, at different doses, as a single agent or in combination with other agents in studies that enrolled more than 13,000 subjects.

Two Phase 3 studies (using 3 mg/kg monotherapy in study MDX010-020 and 10 mg/kg in combination with DTIC in study CA184024) and several Phase 2 studies have demonstrated a favorable benefit: risk ratio for ipilimumab at both the 3 mg/kg dose and the 10 mg/kg dose for the treatment of advanced melanoma.

The safety profile of 3 mg/kg ipilimumab was similar between subjects with previously untreated or treated advanced melanoma and also similar between previously chemotherapy treated or chemotherapy naive subjects. Based on the pooled database of advanced melanoma subjects treated with ipilimumab 3 mg/kg, the rates of AEs, deaths, serious adverse events (SAEs), AEs leading to discontinuation, and irAEs were similar across populations analyzed with no relevant differences observed between previously untreated, previously treated, chemotherapy naive and chemotherapy pretreated subjects with advanced melanoma. The treatment-related adverse events observed in these subjects are consistent with the drug's mechanism of toxicity. The ipilimumab 3 mg/kg data suggests that the AE profile does not appear to be dependent on the type of prior therapy administered to the subject (eg, prior treatment, prior chemotherapy, lines of therapy, etc).

The prognosis of advanced melanoma remains poor and there are limited treatment options, particularly in China. The current standard of care DTIC is associated with significant toxicities and has not been shown in a randomized study to improve survival of patients with advanced melanoma. The proven survival benefit and tolerability of ipilimumab in Western patients supports a head to head comparison of ipilimumab versus DTIC in chemotherapy naive patients with advanced melanoma.

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

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

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

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

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

Before amendment initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The

investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

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

2.3 Informed Consent

Upon approval of this amendment, investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1. Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2. Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
3. Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4. Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5. If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
6. Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed informed consent form (ICF) and, in the US, the subjects' signed HIPAA Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

Subjects unable to give their written consent (eg, stroke or subjects with or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this subject become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a subject who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

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

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is an open-label study to provide ipilimumab to patients eligible for Re-Induction.

The study has enrolled 258 Chinese subjects. Two (2) subjects continue to be followed after having received ipilimumab during the Induction phase. Subjects may be eligible to receive one course of ipilimumab (3 mg/kg) as Re-Induction upon progression, documented per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, if the Re-Induction phase eligibility Criteria outlined below and in Section 3.3.2.1 are met.

This study will close once the 2 patients:

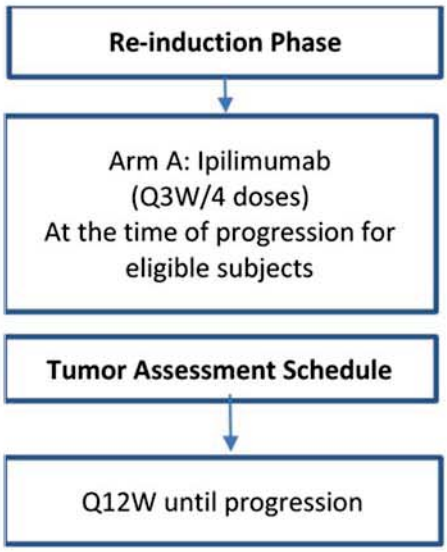
- Complete the Re-Induction schedule of ipilimumab
- Ipilimumab marketing authorization is approved in China — patients will switch to commercial supply 6 months post authorization
- Withdraw consent

Subjects who have completed the Re-Induction schedule of ipilimumab will be followed for a minimum of 90 days and then discontinued from the study.

Discontinue IPI due to PD or toxicities — subjects who have disease progression or toxicities that require permanent discontinuation of ipilimumab in the Re-Induction phase will be followed for a minimum of 90 days and then discontinued from the study.

The study design schematic is presented in Figure 3.1-1.

Figure 3.1-1: Re-Induction Phase Design Schematic



Screening Phase:

This phase has been completed.

Induction Phase:

This phase has been completed.

Re-Induction Phase (only for subjects randomized to ipilimumab):

- Subjects will enter the Re-Induction phase if they meet the following criteria:
  - Initial objective response (partial response [PR] or complete response [CR] - confirmation not required), or stable disease of ≥ 3 months (beginning at Week 12 with SD at Week 24) is achieved after the Induction phase;
  - Subsequent documented progression (per RECIST v1.1)
    - Requires that there is ≥ 20% increase in the sum of longest diameter of all target lesions AND an absolute increase of at least 5 mm of tumor size, taking as reference the smallest sum of the longest diameter recorded at or following baseline or the appearance of one or more new lesions, and;
  - Subjects must meet Re-Induction Inclusion Criteria (as referenced in Section 3.3.2.1);
  - Re-Induction criteria must be reviewed with the BMS Medical Monitor before the Drug Order form is completed and submitted;
- Eligible subjects will receive up to four doses of ipilimumab during Re-Induction (one dose every 3 weeks);
- TAs will be performed every 12 weeks or per standard of care until documented PD or withdrawal of consent. Response assessments during the Re-Induction for the purpose of treatment management decisions will be determined using the most recent tumor assessment prior to the start of the Re-Induction as a new baseline;
- Subjects are eligible to receive one course of Re-Induction therapy only;

- Re-Induction will end when subject withdraws consent, at study closure, or discontinuation of ipilimumab. All subjects will be followed for AEs for a minimum of 90 days following the last dose of ipilimumab (Re-Induction).

End of Treatment Visit:

- Completed when subjects permanently discontinue all study treatments
- The End of Treatment visit may coincide with the visit where the decision to discontinue study treatment was made or may be scheduled as soon as possible after study treatment has been discontinued.

Toxicity/Progression Follow-up Phase:

- Adverse Event assessments will continue until all AEs have resolved, returned to baseline, or are deemed irreversible. All subjects will be followed for AEs for a minimum of 90 days following the last dose of ipilimumab (Re-Induction).

Overall Survival Follow-Up Phase:

Not applicable.

3.1.1 Study Visit Windows

- Treatment Phase visits have a visit window of ± 3 days.
- Study drug dosing for ipilimumab should be three weeks apart (± 3 days);
  - Dosing visits should be scheduled according to the previous dose and the windows calculated according to this date

3.2 Post Study Access to Therapy

Eligible subjects will receive Re-Induction schedule of ipilimumab prior to study closure. The investigator should ensure that the subject receives appropriate standard of care after study closure.

3.3 Study Population

For entry into the study, the following criteria MUST be met.

3.3.1 Inclusion Criteria

Inclusion criteria for the Re-Induction phase are outline in Section 3.3.2.1.

1. **Signed Written Informed Consent**
   a) Willing and able to give written informed consent;
2. **Target Population**
   a) Histologic diagnosis of malignant melanoma;

b) Subject Re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, subject has not been randomized / has not been treated). If re-enrolled, the subject must be re-consented.

c) Chemotherapy naive Stage IV melanoma (AJCC 2010) (regardless of BRAF mutation status) *(Note: prior adjuvant melanoma therapy [eg, IFN therapy], and/or prior treatment with IL-2, BRAF or MEK inhibitor [eg, vemurafenib, dabrafenib, trametinib] in subjects with known BRAF mutation, or cKIT inhibitor [eg, imatinib, nilotinib, or dasatinib] in subjects with cKIT mutation/amplification in the advanced setting is allowed, prior adjuvant chemotherapy is excluded).*

d) Measurable and/or non-measurable disease (as per RECIST v1.1 criteria), within 28 days of first dose of study drug;

e) Life expectancy of ≥ 16 weeks;

f) ECOG performance status of 0 or 1;

g) Have the complete set of baseline (ie, Screening) digital images of lesions and radiographic images, including, but not limited to: brain, chest, abdomen, pelvis and bone scans (only if clinically indicated). All images must be of adequate quality;

h) Required values for initial laboratory tests:

- White blood cells (WBC) ≥ 2500/uL
- Absolute neutrophil count (ANC) ≥ 1500/uL
- Platelets ≥ 100 x 10^3/uL
- Hemoglobin ≥ 9 g/dL
- Serum creatinine ≤ 2.5 × ULN or creatinine clearance (CrCl) ≥ 50mL/min (using the Cockcroft-Gault formula)
- AST / ALT ≤ 2.5 x ULN for subjects without liver metastasis, AST / ALT ≤ 5 x ULN for subjects with liver metastasis
- Bilirubin ≤ 2.5x ULN, (Gilbert's Syndrome allowed, but must have bilirubin < 3 mg/dL)

i) Accessible for treatment and Follow-Up

3. Age and Reproductive Status

a) Chinese males and females ≥ 18 years of age,

Women of childbearing potential (WOCBP) must use method(s) of contraception as indicated in the informed consent form. For a teratogenic study drug and/or when there is insufficient information to assess teratogenicity (preclinical studies have not been done), a highly effective method(s) of contraception (failure rate of less than 1% per year) is required. The individual methods of contraception and duration should be determined in consultation with the investigator. WOCBP subjects that are randomized to ipilimumab must follow instructions for birth control when the half life of the investigational drug is greater than 24 hours; contraception should be continued for a period of 12 weeks after the last dose of investigational product.

Women must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) at Screening and within 24 hours prior to the start of investigational product.

b) Women must not be breastfeeding.

c) Males who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. The investigator shall review contraception methods and the time period that contraception must be followed. Regardless of the treatment arm, men that are sexually active with WOCBP must follow instructions for birth control when the half life of the investigational drug is greater than 24 hours, contraception should be continued for a period of 12 weeks after the last dose of investigational product.

d) Women who are not of childbearing potential (ie, who are postmenopausal or surgically sterile; see Section 3.3.3 for the definition of WOCBP) and azoospermic men do not require contraception.

3.3.2 Exclusion Criteria

Exclusion criteria for the Re-Induction phase are outlined in Section 3.3.2.1.

1. Target Disease Exceptions

a) Evidence of brain metastases on brain imaging (ie, magnetic resonance imaging [MRI] or contrast computed tomography [CT]);

b) Primary ocular or mucosal melanoma;

2. Medical History and Concurrent Diseases

a) Any other malignancy from which the patient has been disease-free for less than 5 years, with the exception of adequately treated and cured basal or squamous cell skin cancer, superficial bladder cancer or carcinoma in situ of the cervix;

b) BRAF status can not be determined by screening test;

c) History of current active autoimmune diseases, including but not limited to Inflammatory Bowel Disease (IBD), rheumatoid arthritis, autoimmune thyroiditis, autoimmune hepatitis, systemic sclerosis (scleroderma and variants), Systemic Lupus Erythematosus (SLE), autoimmune vasculitis, autoimmune neuropathies (eg, Guillain-Barre syndrome). Vitiligo and adequately controlled endocrine deficiencies such hypothyroidism are not excluded ;

d) HIV positive or HBsAg positive, or active Hepatitis C infection, based on testing performed during the screening period of this study.

e) Any underlying medical or psychiatric condition, which in the opinion of the Investigator, will make the administration of study drug hazardous or obscure the interpretation of AEs, such as a condition associated with frequent diarrhea**;**

f) Patients who have had a history of acute diverticulitis, intra-abdominal abscess, GI obstruction and abdominal carcinomatosis which are known risk factors for bowel perforation.

g) History of or current immunodeficiency disease, splenectomy, or splenic irradiation.

h) Prior allogeneic stem cell transplant.

3. Physical and Laboratory Test Findings

a) Not applicable; defined in Inclusion criteria

[redacted]

5. Allergies and Adverse Drug Reaction

a) History of allergic reaction to parenteral administered recombinant protein product;

6. Sex and Reproductive Status

a) WOCBP who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study period and for 12 weeks after the last dose of study therapy.

b) Women who are pregnant or breastfeeding.

c) Women with a positive pregnancy test on enrollment or prior to study drug administration.

d) Sexually active fertile men not using effective birth control, for the entire study period and for 12 weeks after the last dose of study therapy, if their partners are WOCBP.

7. Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated

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

3.3.2.1 Re-Induction Criteria (Only for Subjects Randomized to Ipilimumab)

Subjects who were randomized to the ipilimumab arm may be eligible to enter the Re-Induction phase if they meet the following criteria within 28 days of Re-Induction:

1. Target Population

- Initial objective response (PR or CR, confirmation not required) or stable disease of ≥ 3 months (beginning Week 12 with SD at Week 24) is achieved after the Induction phase *and*
- Subsequent documented progression (per RECIST v1.1)
  - Progressive Disease (PD): Requires that there is ≥ 20% increase in the sum of longest diameter of all target lesions AND an absolute increase of at least 5 mm of tumor size, taking as reference the smallest sum of the longest diameter recorded at or following baseline or the appearance of one or more new lesions.
  - For subjects that have non-measurable disease only at baseline, progression will be determined per (Section 5.4). These subjects are not eligible for Re-Induction if they progress earlier than Week 24.
  - Progressive disease does not require confirmatory scans, however, if the investigator determines that PD is questionable (eg, pseudoprogression), then they may opt to do confirmatory scans no less than 4 weeks since the prior scan in order to verify the reliability of the radiologic finding. Once PD is confirmed, the patient should be re-induced within 28 days and meet all Re-induction eligibility criteria.
- Did not experience any adverse events as described in Section 4.3.2.3 (Permanent Discontinuation of Ipilimumab) or experience a dose delay > 21 days due to toxicity as described in Section 4.3.2.1 (Withholding Dosing of Ipilimumab)
- Did not discontinue ipilimumab for any reason

2. Physical and Laboratory Test Findings

- Meet the following criteria prior to Re-Induction:
  - WBC ≥ 2,500/uL

- Absolute neutrophil count (ANC) ≥ 1,500/uL
- Platelet count ≥ 100,000/uL
- Hemoglobin level ≥ 9 g/dL
- Serum creatinine ≤ 2.5 × ULN or creatinine clearance (CrCl) ≥ 50mL/min (using the Cockcroft-Gault formula)
- Total bilirubin level ≤ 2.5 times the ULN (Gilbert's Syndrome allowed, but must have bilirubin < 3 mg/dL)
- AST and ALT levels ≤ 2.5 times the ULN for subjects without liver metastasis; ≤ 5.0 times the ULN for subjects with liver metastasis.

Eligibility criteria for Re-Induction have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study can be used.

3.3.3 Women of Childbearing Potential

Women of childbearing potential (WOCBP) 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 45 in the absence of other biological or physiological causes. In additional, women under the age of 62 must have a documented serum follicle stimulating hormone, (FSH) level > 40mIU/mL.

- Use of systemic steroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications should be avoided while patients are receiving ipilimumab, except for treatment of immune-related adverse events, replacement of adrenal steroids or premedication specified in the protocol. If systemic steroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications cannot be avoided and will overlap with administration of study drug, the medical monitor should be contacted to discuss potential dose delays of ipilimumab.

Once the subject has entered into the Survival follow-up Phase, then there are no prohibited therapies.

3.4.2 Other Restrictions and Precautions

Refer to Refer to Sections 5.4.11 and.5.4.12

3.5 Discontinuation of Subjects from Treatment

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

- Subject's request to stop study treatment
- Any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Termination of the study by BMS
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Progressive Disease by RECIST v1.1.
- Unacceptable toxicity, as defined in protocol Section 4.3 for ipilimumab, and as defined in the product label for the chosen chemotherapy.

All subjects who discontinue investigational product should comply with protocol specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study treatment is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records.

3.6 Post Treatment Study Follow up

Not applicable.

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study treatment will remain in the study and must continue to be followed for a minimum of 90 days after last ipilimumab dose. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator.

3.6.2 Lost to Follow-Up

Not applicable.

4 TREATMENTS

Study drugs include both Non-investigational Medicinal Products (NIMP) and Investigational Medicinal Products (IMP) and can consist of the following (See Table 4.1-1):

- All products, active or placebo, being tested or used as a comparator in a clinical trial.
- Study required premedication, and
- Other drugs administered as part of the study
- Diagnostic agents: (such as glucose for glucose challenge) given as part of the protocol requirements.

4.1 Study Treatments

Table 4.1-1: Product Description - Ipilimumab (Induction and Re-Induction Phases)

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) / Label Type	Appearance	Storage Conditions (per label)
Ipilimumab Injection, 200 mg/vial	5 mg/mL	40 mL vial, 1-panel, open label	5 vials per box, 1-panel, open label	Clear, colorless liquid. Light (few) particles may be present.	Store refrigerated 2° - 8°C (36° - 46°F). Protect from light, protect from freezing.

4.1.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol amendment, investigational product is: Ipilimumab 5 mg/mL solution.

4.1.2 Non-investigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

In this protocol amendment, non-investigational product is: Not applicable.

4.1.3 Handling and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

For non-investigational product, if marketed product is utilized, it should be stored in accordance with the package insert, summary of product characteristics (SmPC), or similar.

4.2 Method of Assigning Subject Identification

Enrolled subjects have already been assigned a unique identification number.

4.3 Selection and Timing of Dose for Each Subject

4.3.1 Ipilimumab

Ipilimumab will be supplied by BMS.

Subjects randomized to the ipilimumab arm will receive ipilimumab at a dose of 3 mg/kg via a 90-minute infusion every 3 weeks x 4 (Week 1, Week 4, Week 7, and Week 10) unless there is confirmed disease progression (per RECIST v1.1), unacceptable toxicity or any of the other criteria as specified in Section 3.5 are met.

Ipilimumab is to be administered as a 90-minute IV infusion, using a volumetric pump with a 0.2 to 1.2 micron in-line filter at the protocol-specified dose. Alternatively a gravity infusion pump is also allowed provided that the site ensures that the whole planned dose is administered. The drug can be diluted with 0.9% normal saline or 5% Dextrose Injection to concentrations between 1 mg/mL and 4 mg/mL. It is not to be administered as an IV push or bolus injection. Care must be taken to assure sterility of the prepared solutions, since the drug product does not

contain any antimicrobial preservatives or bacteriostatic agents. At the end of the infusion, flush the line with a sufficient quantity of normal saline or 5% dextrose solution;

Ipilimumab injection can be used for IV administration without dilution after transferring to a PVC (polyvinyl chloride), non-PVC/non-DEHP (di-(2-ethylhexyl)phthalate) or glass containers and is stable for 24 hours at 2° - 8ºC or room temperature/room light (RT/RL). For ipilimumab storage instructions, refer to ipilimumab IB and/or pharmacy reference sheets.

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

Infusion volume may be calculated by: total dose in mg divided by 5 mg/mL = infusion volume.

- If the subject weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated.

Refer to the Investigator Brochure and Drug Preparation Guidelines for detailed information.

4.3.2 Dose Modification Criteria - Ipilimumab

4.3.2.1 Withholding Dosing of Ipilimumab

At the discretion of the investigator, it ***may be necessary*** to withhold (maximum 21 days) ipilimumab dosing for the following adverse event(s) considered related to ipilimumab:

- Any Grade 2 non-skin adverse event except for laboratory abnormalities;
- Grade 2 AST, ALT, or Total bilirubin elevation in laboratory values (unless present at baseline);
- Any ≥ Grade 3 laboratory abnormality.

It is necessary to withhold (maximum 21 days) ipilimumab dosing for the following adverse events:

- Any ≥ Grade 3 skin adverse event regardless of causality;
- Any adverse event, laboratory abnormality or intercurrent illness which, in the judgment of the investigator, warrants withholding the dose of study medication.

If treatment must be delay for > 21 days (> 42 days from previous dose), please contact the medical monitor before resuming dosing.

4.3.2.2 Criteria to Resume Treatment with Ipilimumab

When the adverse event(s) resolve(s) to Grade 1 or baseline value, and for endocrinopathies which are controlled with chronic therapy:

- Restart dosing at the next scheduled time point per protocol.
- If the adverse event has not resolved in the protocol-specified dosing window (ie, 3 weeks from last dose ± 3 days), the next scheduled dose will be withheld.

NOTE: Please refer to the most current version of the Ipilimumab Investigator Brochure for algorithms on the management of specific Adverse Events of Interest.

4.3.2.3 Permanent Discontinuation of Ipilimumab

Ipilimumab must be permanently discontinued for any of the following:

1. Adverse event(s) considered related to ipilimumab as described below:
   - Any ≥ Grade 2 eye pain or reduction of visual acuity that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks of starting therapy
     OR requires systemic treatment;
   - Any ≥ Grade 3 bronchospasm or other hypersensitivity reaction;
   - Any other ≥ Grade 3 non-skin adverse event with the exception of laboratory abnormalities and symptomatic endocrinopathies which resolve (with or without hormone substitution); subjects with an adrenal crisis where symptoms resolve (with or without hormone substitution) may resume ipilimumab treatment as well;
   - Any Grade 4 laboratory abnormalities, except AST, ALT, or total bilirubin;
     - AST or ALT > 8 x ULN,
     - Total bilirubin > 5 x ULN;
   - Any other Grade 4 adverse event;
   - Subject experiences an allergic/infusion reaction while receiving study drug at a slower infusion rate due to a prior allergic/infusion reaction;
2. Adverse event(s) regardless of relationship to ipilimumab as described below:
   - Any motor neurologic toxicity ≥ Grade 3 regardless of causality;
   - Any adverse event, laboratory abnormality or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued study drug dosing;
   - Any ≥ Grade 3 treatment related sensory neurologic toxicity;
3. Drug related toxicity that prevents administration of ipilimumab for > 21 days from the scheduled dose.
4. Confirmed and documented progression of disease on ipilimumab retreatment, per RECIST v1.1 criteria.

Experience is limited for continuing ipilimumab in subjects who have experienced Grade 3 - 4 endocrine toxicities (eg, adrenal crisis). In these situations, the medical monitor should be consulted before continuing treatment with ipilimumab.

4.3.3 Treatment of Study Drug Related Infusion Reaction

Infusion reactions should be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 allergic reaction/hypersensitivity

criteria. Severe infusion reactions require the immediate interruption of study drug therapy and permanent discontinuation from further treatment.

Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Subjects should be carefully observed until the complete resolution of all signs and symptoms. In each case of an infusion reaction, the investigator should institute treatment measures according to the best available medical practice and institutional norms.

The following treatment guidelines are suggested:

CTCAE Grade 1 Allergic reaction/hypersensitivity (transient flushing or rash, drug fever < 38°C).

- Treatment: Decrease the study drug infusion rate by 50% and monitor closely for any worsening.

CTCAE Grade 1 or Grade 2 Allergic reaction/hypersensitivity manifesting only as delayed drug fever (starting after the completion of the study drug infusion).

- Treatment: Maintain study drug dose and infusion rate for future infusions. Consideration could be given to administration of acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID) prior to the subsequent study drug infusion, if not otherwise contraindicated in subjects. Dose and schedule of these agents is entirely at the investigator's discretion.

CTCAE Grade 2 Allergic reaction/hypersensitivity (rash, flushing urticaria, dyspnea, drug fever ≥ 38°C).

- Treatment: Interrupt study drug infusion. Administer bronchodilators, oxygen, etc as medically indicated. Resume infusion at 50% of previous rate once infusion reaction has resolved or decreased to Grade 1 in severity, and monitor closely for any worsening.

CTCAE Grade 3 or Grade 4 Allergic Reaction/Hypersensitivity: A CTCAE Grade 3 hypersensitivity reaction (symptomatic bronchospasm, requiring parenteral medication(s), with or without urticaria; allergy-related edema/ angioedema; hypotension) or a Grade 4 hypersensitivity reaction (anaphylaxis).

- Treatment: Stop the study drug infusion immediately and disconnect infusion tubing from the subject. Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc, as medically indicated. Contact the Medical Monitor and document as a serious adverse event (Section 6.1). No further study drug treatment to be administered.

4.3.3.1 Re-treatment with Study Drug Following Infusion Reactions

Once the study drug infusion rate has been decreased due to an infusion reaction, it will remain decreased for all subsequent infusions. If the subject has a second allergic/infusion reaction at the slower infusion rate, the infusion should be stopped and the subject should be discontinued from study drug. If a subject experiences a Grade 3 or 4 allergic/infusion reaction at any time, the subject should be discontinued from study drug. If there is any question as to whether an observed reaction is an allergic/infusion reaction of Grades 1 - 4, the Medical Monitor should be contacted immediately to discuss and grade the reaction.

4.3.3.2 Treatment of Ipilimumab Related Isolated Drug Fever

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

4.4 Blinding/Unblinding

Not applicable.

4.5 Treatment Compliance

Treatment compliance will be assessed by investigator.

4.6 Destruction and Return of Study Drug

4.6.1 Destruction of Study Drug

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The

method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.

- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met the responsible BMS will make arrangements for return of study drug.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.6.2 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible BMS personnel.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Procedural Outline - Re-Induction Phase (CA184248)

Procedure	Re-Induction Phase (ipilimumab arm only) (± 3 days)						End of Treatment Visit	Toxicity/ Progression Follow-up (± 14 days)	Notes
	D1/ W1	D22/ W4	D43/ W7	D64/ W10	D78/ W12	D162/ W24			
Safety Assessments									
Physical Examination	X	X	X	X			X		Per Standard of Care (SOC).
Vital Signs	X	X	X	X					Per Standard of Care (SOC).
Weight	X	X	X	X					
ECG (12 lead)									Required as clinically indicated.
ECOG PS	X	X	X	X			X		
Concomitant Medications	X	X	X	X	X	X	X	X	
Serious Adverse Events Assessment	X	X	X	X	X	X	X	X	
Adverse Events Assessment	X	X	X	X	X	X	X	X	

Table 5.1-1: Procedural Outline - Re-Induction Phase (CA184248)

Procedure	Re-Induction Phase (ipilimumab arm only) (± 3 days)						End of Treatment Visit	Toxicity/ Progression Follow-up (± 14 days)	Notes
	D1/ W1	D22/ W4	D43/ W7	D64/ W10	D78/ W12	D162/ W24			
Laboratory Tests									
Hematology, Chemistry	X	X	X	X			X		Results of safety laboratory collections (ie, Chemistry and Hematology) must be obtained and reviewed prior to dosing.
Endocrine	X	X	X	X					Section 5.3.7.3
HIV, hepatitis C antibody, hepatitis B surface antigen (HBsAg)									To be repeated during the course of the study if clinically indicated.
Pregnancy Test	X	X	X	X			X		Section 3.3 Women of childbearing potential must have a negative pregnancy test within 24 hours prior to study drug dosing.
Efficacy Assessments									
Section 5.4.2.1. Tumor assessments will be based on RECIST v1.1 criteria. Confirmatory scans are not required. TAs will be performed every 12 weeks or per standard of care until documented PD or withdrawal of consent.									
Clinical Drug Supplies									
Ipilimumab	X	X	X	X					Subjects are eligible to receive only one course of Re-Induction therapy only

5.1.1 Retesting During Screening or Lead-in Period

Not applicable.

5.2 Study Materials

In-line infusion filters will be obtained locally by the site, except where prohibited by local regulations. See the current Investigator Brochure for additional information on allowable filter types.

The sponsor (or designee) will also supply:

- Ipilimumab Investigator Brochure
- Drug Preparation Guidelines
- Laboratory Manuals
- Drug Order Form
- BMS SAE Reporting Form
- Pregnancy Surveillance Form

5.3 Safety Assessments

All subjects who receive at least 1 dose of study treatment (ipilimumab) will be evaluated for safety parameters. Additionally, any occurrence of an SAE from the time of consent forward will be documented.

Safety will be evaluated for all treated subjects using the NCI CTCAE version 5.0. Safety assessments will be based on medical review of AE reports and the results of vital sign measurements, physical examinations, and clinical laboratory tests. For details of the planned safety analyses, see Section 8.4.2.

Additional procedures and assessments may be performed as part of standard of care however data for these assessments should remain in the subject's medical record and should not be provided to BMS, unless specifically requested by the sponsor.

BMS may request that survival data be collected on all treated/randomized subjects outside of the protocol defined window (Table 5.1-1). At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contact.

5.3.1 Imaging Assessment for the Study

Imaging will be assessed per standard of care.

5.3.2 Medical History, Physical Exam, Physical Measurements

Physical Exam and measurements will be assessed as per standard of care. Medical history was already reported in Induction phase of the study.

5.3.3 Vital Signs

Vital signs will be assessed per standard of care. Recommendations are below.

- Ipilimumab: During ipilimumab infusions, it is recommended that vital sign measurements (pulse and systolic and diastolic BP) will be reviewed prior to dosing and every 30 minutes for the duration of the infusion (ie, 30 minutes, 60 minutes and 90 minutes after start of the infusion).

5.3.4 ECG

Required as clinically indicated.

5.3.5 Pregnancy Testing

WOCBP are required to have pregnancy tests performed. A negative pregnancy test must be documented at the Screening visit. Additionally, WOCBP must exhibit a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug (ipilimumab).

In addition, a pregnancy test (serum or urine with a minimum sensitivity 25 IU/L or equivalent units of HCG) must be performed within 24 hours prior to dosing at every study drug (ipilimumab) administration visit.

5.3.6 ECOG Performance Status

Eastern Cooperative Oncology Group (ECOG) Performance Status will be evaluated as outlined in Section 5.1.

5.3.7 Laboratory Testing

All protocol specified laboratory tests will be analyzed and reported by the local lab.

Laboratory tests are obtained as part of screening and to determine eligibility. Results of safety laboratory collections (ie, Chemistry and Hematology) will be reviewed in advance of study drug dosing.

5.3.7.1 Chemistry

Serum chemistry will be obtained as outlined in Section 5.1.

Serum chemistry tests will include:

- Albumin
- Amylase (lipase should be monitored when amylase is abnormal with clinical significance)
- Urea or BUN
- Creatinine
- ALT
- AST
- Total bilirubin (direct bilirubin tested as clinically indicated, ie, elevated total bilirubin)
- C-reactive protein (CRP)
- LDH
- Serum alkaline phosphatase

- Glucose
- Total protein
- Potassium
- Sodium
- Chloride
- Calcium.
- Phosphorus
- Uric acid

Additional draws must be incorporated when monitoring recovery from any nonhematologic AE (eg, elevations in ALT, AST).

At the treatment visits, the samples for the chemistry panel need to be collected prior to dose administration of study drug.

Samples for LFT results (AST, ALT, and total bilirubin) must be reviewed within 3 days prior to dosing. If abnormal LFTs are detected, the subject must be managed using the hepatoxicity algorithm in the Investigator's Brochure. (Additional draws must be incorporated when monitoring recovery from any non-hematologic AE (eg, elevations in ALT, AST).

Note: LFTs (ALT, AST, and total bilirubin) must be performed within 3 days prior to each ipilimumab dosing visit. Results of the LFTs must be reviewed by the principal investigator (or designee) prior to ipilimumab dosing.

5.3.7.2 Hematology

A complete blood count (CBC) with differential will be obtained as outlined in Section 5.1.

Hematology labs will routinely include:

- Hemoglobin
- Hematocrit
- Red blood cell count
- White blood cell count and differential counts
- Platelets (direct platelet count).
- Differential counts. The CBC differential includes enumeration of:
  - neutrophils,
  - lymphocytes,
  - eosinophils,
  - monocytes,
  - basophils,
  - any atypical blood cells.

Additional draws must be incorporated when monitoring recovery from any hematologic AE.

Note: CBC with differential, including absolute lymphocyte count, must be collected within 3 days prior to each ipilimumab dosing visit. Results of these tests must be reviewed by the principal investigator (or designee) prior to dosing.

Note: If any part of the laboratory differential is related to an AE, SAE, or change in treatment, provide the complete differential (neutrophils, lymphocytes [absolute lymphocyte count], eosinophils, monocytes, basophils, bands and any atypical cells) and WBC (leukocyte) results.

5.3.7.3 Endocrine Tests

The following endocrine tests should be performed as outlined in Section 5.1:

- TSH
  - prior to each ipilimumab dosing visit
- Free T3 and T4
  - as clinically indicated.

5.3.7.4 HIV and Hepatitis Panel

These tests will be repeated during the course of the Re-Induction phase if clinically indicated:

- HIV antibody
- Hepatitis C antibody,
- HBsAg.

5.4 Efficacy Assessments

5.4.1 Primary Efficacy Assessment

The primary endpoint of this study was the 2-year OS rate. The database lock for this endpoint was 03Jun2019.

5.4.2 Secondary Efficacy Assessment

Secondary response-based endpoints of OS, PFS, disease control rate, duration of response, duration of stable disease, and BORR were captured using the RECIST v1.1 criteria.

Tumor response was based on investigator assessment. During the Induction Phase tumor assessments were performed at Screening and at Weeks 12, 18 and 24.

The database lock was 03Jun2019 for these endpoints.

Re-Induction phase:

For patients eligible for Re-Induction, PD must be reviewed with the BMS Medical Monitor before the Drug Order Form is submitted.

During the Re-Induction phase, tumor assessments will be performed every 12 weeks or per standard of care until documented PD or withdrawal of consent.

During the Re-Induction phase, subjects who have progressed and come off of study therapy (ipilimumab) due to toxicity will be followed for a minimum of 90 days for AEs and then will discontinue from the study.

5.4.2.1 Radiographic Assessments

CT or MRI imaging of the chest and abdomen were required at Screening (ie, Baseline) and at each tumor assessment visit, regardless of the location of known metastases.

CT/MRI imaging of the pelvis was only required at baseline and thereafter as clinically indicated.

Brain scans were required at Screening. Brain scans will also be repeated during the study when clinically indicated. MRIs are preferred, contrast enhanced CTs are a second choice.

Similar methods of tumor assessment and similar techniques must be used to characterize each identified and reported lesion at Screening and during the Induction and Re-Induction phases. Imaging-based evaluation is preferred to clinical examination.

Helical (spiral) CT scans of chest and abdomen are preferred. If not available, conventional (non-helical, non-spiral CT) should be used.

If not contraindicated, i.v. contrast should be used for all studies. If i.v. contrast is contraindicated, MRI should be used at the Screening exam and at all tumor assessment time points.

Oral contrast should be used for all applicable imaging unless contraindicated.

Should a subject develop allergy to contrast, the subject should be allowed to have the option to use Non-contrast CT scan.

A reference measurement ruler must be printed on every image for scale determination. Sections should be contiguous, similarly sized and consistent from visit-to-visit.

Section thickness must be based on institutional standards (eg, from 5 to 8 mm, 10 mm cuts are not recommended). Ultrasound is not acceptable method to measure disease. Response and progression of disease must be documented by CT or MRI similar to the methods used at Screening.

Neither response nor progressive disease will require confirmatory scans, however, if the investigator determines that PD is questionable (eg, pseudoprogression), then they may opt to do confirmatory scans in order to verify the progression.

Bone scans can be performed as clinically indicated at screening or specified tumor assessment points.

5.4.2.2 Non-radiographic Assessments

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers.

For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. When lesions can be evaluated both by clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

5.4.3 Assessment of Overall Tumor Burden

Baseline assessments should be performed within 28 days prior to Re-Induction utilizing CT or MRI. In addition to chest, abdomen, pelvis, and brain, all known sites of disease should be assessed. Subsequent assessments should include chest, abdomen, and pelvis, and all known sites of disease and should use the same imaging method as was used as baseline.

5.4.3.1 Measurable Lesions

Measurable lesions must be accurately measured in at least one dimension (longest diameter in the plane of the measurement to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

5.4.3.2 Non-Measureable Lesions

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis, as well as truly nonmeasurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphagitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

5.4.3.3 Special Considerations Regarding Lesion Measurability

Bone Lesions:

- Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are by definition, simple cyst.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same subject, these are preferred for selection as target lesions.

Lesions with prior treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to locoregional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

5.4.4 Specification by Method of Measurement

5.4.4.1 Measurement of Lesions

All measurements should be recorded in the metric notation (mm). All baseline evaluations should be performed as close as possible to the Re-Induction treatment start and never more than 28 days before the beginning of treatment.

5.4.4.2 Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions:

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As previously noted, when lesions can be evaluated both by clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray:

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT/MRI:

CT is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations.

Ultrasound:

Ultrasound is not useful in the assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Endoscopy, laparoscopy:

The utilization of these techniques for objective tumor evaluation is not advised.

Tumor markers:

Tumor markers alone cannot be used to assess objective tumor response.

5.4.5 Baseline Documentation of "target" and "non-target" lesions

5.4.5.1 Target Lesions

Target lesions were recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should lend themselves to reproducible repeated measurements.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted below, only the short axis is added into the sum. The baseline

sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

5.4.5.2 Lymph Nodes

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

5.4.5.3 Non-target Lesions

Non-target lesions were recorded at baseline.

5.4.6 Tumor Response Evaluation

5.4.6.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

5.4.6.2 Special Notes on the Assessment of Target Lesions

Lymph nodes:

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded and should be measured in the same anatomical plane as the baseline examination, even if the nodes regress to below 10 mm 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 < 10 mm.

Target lesions that become 'too small to measure':

All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). If the radiologist is able to provide an actual measurement, that should be recorded, even if it is below 5 mm.

However, when such a lesion becomes difficult to assign an exact measure to then:

(i) If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.

(ii) If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (note: in case of a lymph node believed to be present and faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).

(iii) Lesions that split or coalesce on treatment:

When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum.

As lesions coalesce, a plane between them maybe maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

5.4.6.3 Evaluation of Non-target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) above the normal limits.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions (Note: the appearance of one or more new lesions is also considered progression).

5.4.6.4 Unequivocal Progression in Non-target Disease

To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

5.4.7 New Lesions

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of preexisting lesions. This is particularly important when the subject's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan reported as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the subject who has visceral disease at baseline and while on study has a CT or MRI brain scan ordered which reveals metastases. The subject's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

5.4.8 Response Criteria (RECIST 1.1)

For subjects who had measurable disease at baseline, Table 5.4.8-1 provides a summary of the overall response status calculation at each time point.

Table 5.4.8-1: Time Point Response - Subjects with Target (±Non-target) Disease

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease, NE = Not Evaluable

5.4.8.1 Missing Assessments and Not Evaluable Designation

Not applicable in the Re-Induction phase.

5.4.8.2 Confirmation of Scans

Verification of Response: Confirmation of response is not required since it will not add value to the interpretation of study results per RECIST 1.1.

Verification of Progression: Progression of disease should be verified in cases where progression is equivocal. If repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the subject is considered not to have progressive disease per RECIST 1.1.

5.4.9 Best Overall Response

The best overall response is determined once all the data for the subject is known. It is defined as the best response designation, as determined by the investigator, recorded between the date of randomization and the date of objectively documented progression per RECIST v1.1 or the date of subsequent therapy, whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment. The subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

For purposes of this study, the minimum scan time from baseline for determination of SD will be 8 weeks.

5.4.10 Duration of Response

Duration of response:

The duration of response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

Duration of stable disease:

Stable disease is measured from the start of the randomization date until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

5.4.11 Surgical Resection Following Initial Response

Investigators may choose to resect solitary lesions in subjects with Stage IV melanoma and render the subject free of macroscopic disease. Subjects with a PR who go on to have surgical resection of remaining disease will be considered a PR.

5.4.12 Local Radiotherapy for Symptomatic Bone Lesions

Local radiation treatment to the site of bone metastasis will be permitted for palliative pain management at any time during the study but it is encouraged that the Investigator perform this local radiotherapy following consultation with the Medical Monitor.

5.5 Pharmacokinetic Assessments

Not applicable.

5.6 Biomarker Assessments

Not Applicable

5.7 Outcomes Research Assessments

Outcomes Research Assessment will not be collected during the Re-Induction phase.

Assessments listed below were collected in the Induction phase of the study.

Reducing mortality and morbidity is still the most important factor in clinical research.

Nevertheless, issues such as reducing side effects, symptom relief and improving subjects' satisfaction have also become relevant parameters in the evaluation of medical strategies. Cancer treatments may produce adverse effects and diminish the HRQoL even when survival is extended. Progress in the acceptance of new cancer therapies is sometimes critically dependent on their HRQoL consequences.

HRQoL is a multidimensional concept, which represents the physiological, psychological and social influences of the disease and the therapeutic process from the subjects' perspective. It comprises four principal components: physical, psychological and social well-being and daily life functioning.

The HRQoL questionnaires to be used for this study are described below.

5.7.1 European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30

The EORTC QLQ-C30 (Appendix 2) is a 30-item, self-administered, multi-dimensional, cancer-specific HRQoL: questionnaire that measures: global health status (2 items), functional scales (15 total items within 5 domains), and symptom scales (13 items).[24]

For questions under the functional and symptom scales, subjects respond to each item on a 4-point Likert-type scale ranging from 1 (not at all) to 4 (very much). For questions under global health status, subjects respond to each item on a 7-point Likert-type scale ranging from 1 (very poor) to 7 (excellent). On average, the questionnaire can be completed in less than 10-15 minutes. Assessment of HRQoL will be conducted at each site with the appropriately translated and validated version of the EORTC QLQ-C30. All scales and single items meet the standards for reliability. The reliability and validity of the questionnaire is highly consistent across different language-cultural groups.

The EORTC QLQ-C30 will be collected at the following visits: Weeks 1, 4, 7, 10, 12, 18, and 24, and End of Treatment.

5.7.2 European Quality of Life-5 Dimensions (EQ-5D) Questionnaire

EQ-5D (Appendix 3) is a standardized measure of health status developed by the EuroQoL Group in order to provide a simple, generic measure of health for clinical and economic appraisal.[25]

EQ-5D essentially consists of the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, severe problems. The respondent is asked to indicate his/her health state by ticking (or placing across) in the box against the most appropriate statement in each of the 5 dimensions. The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled 'best imaginable health state' and 'worst imaginable health state'. This information can be used as a quantitative measure of health

outcome as judged by the individual respondents. The indirect estimates of health-related utilities provided by the EQ5D will enable an assessment of the consistency of the health state descriptions with clinical reality. This may mitigate any concerns over the use of a convenience sample of the general public used in other subject preference studies.

The EQ-5D will be collected at the following visits: Weeks 1, 4, 7, 10, 12, 18, and 24, and End of Treatment.

5.7.3 Health Related Resource Utilization

Health Related Resource utilization data will not be collected.

5.8 Results of Central Assessments

Not applicable.

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (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.

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

> Related: There is a reasonable causal relationship between study drug administration and the AE.
>
> Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

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

6.1 Serious Adverse Events

A ***Serious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)

- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

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

Although pregnancy, overdose, and cancer are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (see Section 6.1.1 for reporting details).

NOTE:

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

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

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 90 days of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

The investigator should report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure on the BMS GPVE form RD-FRM-SOP-006991-5.

The paper form (GPVE form RD-FRM-SOP-006991-5) should be submitted immediately, within 24 hours. The original paper forms are to remain on site. Pregnancies are to be reported on a Pregnancy Surveillance Form RD-FRM-SOP-006991-4 [007177] paper form).

The paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: worldwide.safety@bms.com

SAE Facsimile Transmission, Central Facsimile Station: 609-818-3804

SAE Global 24 hour telephone number: International: +1-248-844-7390

SAE Telephone Contact (required for SAE and pregnancy reporting): Refer to Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

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

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

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

6.2.1 Nonserious Adverse Event Collection and Reporting

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All nonserious AEs that are not listed in the IB as expected must be recorded and described on the nonserious AE page of the GPVE form RD-FRM-SOP-006991-5.

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the GPVE form RD-FRM-SOP-006991-5, as appropriate:

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

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

These procedures are considered standard of care and are recommended, but are not mandatory.

6.4 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS, the pregnant subject may continue study drug after a thorough discussion of benefits and risk with the subject.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS Medical Monitor (or designee) of this event and complete and forward a Pregnancy Surveillance Form (RD-FRM-SOP-006991-4 [007177] paper form) to BMS (or designee) within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

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

6.5 Overdose

All occurrences of overdose must be reported as SAEs (see Section 6.1.1 for reporting details).

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

6.6 Adverse Events of Interest

Adverse events of interest are AEs consistent with an immune mediated mechanism and include enterocolitis, dermatitis, hepatitis, endocrinopathies and neuropathies, although other less common immune mediated AEs have been reported as well. The severity of these immune mediated AEs may range from mild to severe and life threatening.

These AEs of interest will be evaluated as follows:

- **Immune-related adverse events (irAEs)**: These are AEs that are 1) AEs of interest (per description above) and 2) drug related by the investigator.
- **Immune-mediated adverse reactions (imARs)**: AEs of special interest will also be adjudicated by the investigator as an imAR (yes) or not an imAR (no) or unknown. The rationale for imAR adjudication is in Section 1.4.1.

The characterization of an AE as an imAR or not is based on retrospective review of the AE that takes into account the context (eg, concomitant therapies, medical history, etc), evaluation, treatment and outcome. Therefore, for purposes of managing an AE, the investigator should refer to the guidance in the protocol (provided in Section 4.3) and Investigator Brochure for evaluation and treatment and not use the case definitions. Data relative to these evaluations and interventions must be included in the source documentation. The complete case definitions for classifying AEs as an imAR are provided as an Appendix in the IB, however in general:

1. AEs of interest should first be evaluated for exclusion as an imAR:

- Typical reasons an event is not considered an imAR
  - Likely due to concomitant drug/chemotherapy/radiation and thus unlikely an imAR
  - Documented evidence of tumor, tumor progression, or tumor related as the most likely cause of the event
  - Same grade event at baseline/medical history/pre-treatment event
  - Event likely caused by infection, or other disease process (eg, infection) or etiology
  - Resolves in less than 1 week without immunosuppression (a definition based on review of resolution for immune mediated AEs of interest from ipilimumab program) suggests that the AE is not an imAR
  - Other reasons may also be valid (see Investigator Brochure, Case Definitions).

2. If the investigator is unable to exclude then the AE of interest should be evaluated as an imAR:

- Typical reasons an event is considered an imAR:
  - Inflammation per pathology or endoscopy
  - Radiologic, imaging, laboratory, or other diagnostic procedure the provides or suggest evidence of an inflammatory process
  - Improves/resolves after immunosuppression (eg, favorable evolution when treated by immunosuppressive drugs supports the AE to be an imAR.)
  - Similar to previous imAR in same organ (based on clinical data from ipilimumab program that imARs may recur in same organ
  - Other reasons may also be valid such as AE persists greater than 1 week or worsens (see Investigator Brochure, Case Definitions).

Occasionally, AEs of interest will not have enough information to classify as imAR or not, in which case, the AE should be classified as unknown whether imAR.

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

Not Applicable.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

There are two patients eligible for Re-induction.

8.2 Populations for Analyses

No analysis will be conducted.

8.3 Endpoints

Not applicable.

8.3.1 Safety

Safety data need to be collected until 90 days after the last dose of study medication is received.

8.4 Analyses

8.4.1 Efficacy Analyses

Not applicable.

8.4.2 Safety Analyses

No safety analysis will be conducted.

8.4.3 Pharmacokinetic Analyses

Not applicable.

8.4.4 Biomarker Analyses

Not Applicable.

8.4.5 Outcomes Research Analyses

Not Applicable.

8.4.6 Other Analyses

Not Applicable.

8.4.7 Interim Analyses

Not applicable.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Amendment

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

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

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations

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

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

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to amendment initiation. Training topics will include but are not limited to: GCP, AE reporting, study details

and procedure, study documentation, drug ordering, safety reporting, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

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

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

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation.

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

9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected considering the following criteria:

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team).

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to BMS at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

10 GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or BMS as related to the investigational product
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator Brochure for an unapproved investigational product)
Serious Adverse Event	Serious adverse event defined as any untoward medical occurrence that at any dose: results in death; is life threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe), requires inpatient hospitalization or causes prolongation of existing hospitalization; results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect; is an important medical event (defined as a medical event(s) that may not be immediately life threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.). For reporting purposes only, BMS also considers the occurrence of pregnancy, overdose (regardless of association with an AE), and cancer as important medical events.

11 LIST OF ABBREVIATIONS

Term	Definition
ADA	anti-drug antibody
AE	adverse event
ALM	Acral lentiginous melanoma
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APC	antigen presenting cells
AST	aspartate aminotransferase
BA/BE	bioavailability/bioequivalence
BLA	Biologic License Agreement
BMS	Bristol-Myers Squibb
BOR	best overall response
BORR	best overall response rate
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen
C	Celsius
CBC	complete blood count
CDE	Center for Drug Evaluation
CFR	Code of Federal Regulations
CI	confidence interval
CL	clearance
CMH	Cochran-Mantel-Haenszel
CR	complete response
CRF	Case Report Form, paper or electronic
CRP	C-reactive protein
CT	computed tomography
CTA	clinical trial agreement
CTCAE	Common Terminology Criteria for Adverse Events

Term	Definition
CTLA-4	cytotoxic T-lymphocyte-associated antigen 4
DC	dendritic cells
DCR	disease control rate
dL	deciliter
DTIC	Dacarbazine
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eg	exempli gratia (for example)
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D	European Quality of Life-5 Dimensions
E-R	exposure-response
EU	European Union
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	Human Immunodeficiency Virus
HR	hazard ratio
HRQoL	Health Related Quality of Life
IBW	ideal body weight
ICF	informed consent form
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IL/U	international units

Term	Definition
imAR	immune-mediated adverse reaction
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
irAEs	Immune-related AEs
IRB	Institutional Review Board
IV	intravenous
IVRS	interactive voice response system
kg	kilogram
LDH	lactate dehydrogenase
MHC	major histocompatibility complex
mg	milligram
MCM	mucosal melanoma
mm	millimeter
MRI	magnetic resonance imaging
n	number, count
N/A	not applicable
NCI	National Cancer Institute
NIMP	non-investigational medicinal products
NM	nodular melanoma
Non-CR	Non complete response
Non-PR	Non partial response
NSAID	nonsteroidal anti-inflammatory drug
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	Progression Free Survival
PK	pharmacokinetics
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan

Term	Definition
SD	stable disease
SEER	Surveillance Epidemiology and End Result
SFDA	State Food and Drug Administration
SOP	Standard Operating Procedures
SSM	superficial spread melanoma
TA	tumor assessment
TCR	T cell-receptor
TMZ	Temozolomide
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States
US NCCN	US National Comprehensive Cancer Network
VAS	visual analog scale
Vd	volume of distribution
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

APPENDIX 1 ECOG PERFORMANCE STATUS

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

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

APPENDIX 2 EORTC QLQ-C30 (VERSION 3)

EORTC QLQ-C30

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: αααα
Your birthdate (Day, Month, Year): βδβδβχχδ
Today's date (Day, Month, Year): 31 βδβδβχχδ

	NOT AT ALL	A LITTLE	QUITEA BIT	VERY MUCH
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
DURING THE PAST WEEK:	**NOT AT ALL**	**A LITTLE**	**QUITEA BIT**	**VERY MUCH**
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4

9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4

DURING THE PAST WEEK:	NOT AT ALL	A LITTLE	QUITEA BIT	VERY MUCH
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

APPENDIX 3 EQ-5D HEALTH QUESTIONNAIRE

Health Questionnaire
English version for the UK (validated for Ireland)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

1) Mobility

I have no problems in walking about	☐
I have some problems in walking about	☐
I am confined to bed	☐

2) Self-Care

I have no problems with self-care	☐
I have some problems washing or dressing myself	☐
I am unable to wash or dress myself	☐

3) Usual Activities (e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities	☐
I have some problems with performing my usual activities	☐
I am unable to perform my usual activities	☐

4) Pain/Discomfort

I have no pain or discomfort	☐
I have moderate pain or discomfort	☐
I have extreme pain or discomfort	☐

5) Anxiety/Depression

I am not anxious or depressed	☐
I am moderately anxious or depressed	☐
I am extremely anxious or depressed	☐

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today